

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 February 2003 (13.02.2003)

PCT

(10) International Publication Number
WO 03/012082 A2

- (51) International Patent Classification⁷: C12N 5/06, 15/11, A61K 48/00, 31/70
- (74) Agent: HARRISON GODDARD FOOTE; 31 St Saviourgate, York YO1 8NQ (GB).
- (21) International Application Number: PCT/GB02/03409
- (22) International Filing Date: 25 July 2002 (25.07.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0118223.7 26 July 2001 (26.07.2001) GB
- (71) Applicant (*for all designated States except US*): **AXORDIA LIMITED** [GB/GB]; Firth Court, Western Bank, Sheffield S10 2TN (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **ANDREWS, Peter** [GB/GB]; University of Sheffield, Western Bank, Sheffield S10 2TN (GB). **WALSH, James** [GB/GB]; University of Sheffield, Western Bank, Sheffield S10 2TN (GB). **GOKHALE, Paul** [GB/GB]; University of Sheffield, Western Bank, Sheffield S10 2TN (GB).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— *without international search report and to be republished upon receipt of that report*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 03/012082 A2

(54) Title: METHOD FOR MODULATING STEM CELL DIFFERENTIATION USING STEM LOOP RNA

(57) Abstract: This invention relates to a method to promote the differentiation of stem cells, typically embryonic stem cells, through the use of RNA interference, by the introduction of stem loop RNA into a cell.

Method for Modulating Stem Cell Differentiation Using Stem Loop RNA

The invention relates to a method to modulate stem cell differentiation comprising introducing stem loop containing RNA into a stem cell to ablate mRNA's which
5 encode polypeptides which are involved in stem cell differentiation; stem loop RNA's ; and nucleic acid molecules and vectors encoding stem loop RNA's.

A number of techniques have been developed in recent years which purport to specifically ablate genes and/or gene products. For example, the use of anti-sense
10 nucleic acid molecules to bind to and thereby block or inactivate target mRNA molecules is an effective means to inhibit the production of gene products. This is typically very effective in plants where anti-sense technology produces a number of striking phenotypic characteristics. However, antisense is variable leading to the need to screen many, sometimes hundreds of, transgenic organisms carrying one or
15 more copies of an antisense transgene to ensure that the phenotype is indeed truly linked to the antisense transgene expression. Antisense techniques, not necessarily involving the production of stable transfectants, have been applied to cells in culture, with variable results.

20 In addition, the ability to be able to disrupt genes via homologous recombination has provided biologists with a crucial tool in defining developmental pathways in higher organisms. The use of mouse gene "knock out" strains has allowed the dissection of gene function and the probable function of human homologues to the deleted mouse genes, (Jordan and Zant, 1998).

25 A much more recent technique to specifically ablate gene function is through the introduction of double stranded RNA, also referred to as inhibitory RNA (RNAi), into a cell which results in the destruction of mRNA complementary to the sequence included in the RNAi molecule. The RNAi molecule comprises two complementary
30 strands of RNA (a sense strand and an antisense strand) annealed to each other to

form a double stranded RNA molecule. The RNAi molecule is typically derived from exonic or coding sequence of the gene which is to be ablated.

Surprisingly, only a few molecules of RNAi are required to block gene expression
5 which implies the mechanism is catalytic. The site of action appears to be nuclear as little if any RNAi is detectable in the cytoplasm of cells indicating that RNAi exerts its effect during mRNA synthesis or processing.

The exact mechanism of RNAi action is unknown although there are theories to
10 explain this phenomenon. For example, all organisms have evolved protective mechanisms to limit the effects of exogenous gene expression. For example, a virus often causes deleterious effects on the organism it infects. Viral gene expression and/or replication therefore needs to be repressed. In addition, the rapid development of genetic transformation and the provision of transgenic plants and animals has led
15 to the realisation that transgenes are also recognised as foreign nucleic acid and subjected to phenomena variously called quelling (Singer and Selker, 1995), gene silencing (Matzke and Matzke, 1998) , and co-suppression (Stam et. al., 2000).

Initial studies using RNAi used the nematode *Caenorhabditis elegans*. RNAi
20 injected into the worm resulted in the disappearance of polypeptides corresponding to the gene sequences comprising the RNAi molecule (Montgomery et. al., 1998; Fire et. al., 1998). More recently the phenomenon of RNAi inhibition has been shown in a number of eukaryotes including, by example and not by way of limitation, plants, trypanosomes (Shi et. al., 2000) *Drosophila spp.* (Kennerdell and Carthew, 2000).
25 Recent experiments have shown that RNAi may also function in higher eukaryotes. For example, it has been shown that RNAi can ablate *c-mos* in a mouse oocyte and also E-cadherin in a mouse preimplantation embryo (Wianny and Zernicka-Goetz, 2000).

30 The use of RNAi to ablate stem cell RNA is disclosed in our co-pending application, WO 02/16620, which is incorporated by reference.

During mammalian development those cells that form part of the embryo up until the formation of the blastocyst are said to be totipotent (e.g. each cell has the developmental potential to form a complete embryo and all the cells required to support the growth and development of said embryo). During the formation of the blastocyst, the cells that comprise the inner cell mass are said to be pluripotent (e.g. each cell has the developmental potential to form a variety of tissues).

Embryonic stem cells (ES cells, those with pluripotentiality) may be principally derived from two embryonic sources. Cells isolated from the inner cell mass are termed embryonic stem (ES) cells. In the laboratory mouse, similar cells can be derived from the culture of primordial germ cells isolated from the mesenteries or genital ridges of days 8.5-12.5 *post coitum* embryos. These would ultimately differentiate into germ cells and are referred to as embryonic germ cells (EG cells). Each of these types of pluripotent cell has a similar developmental potential with respect to differentiation into alternate cell types, but possible differences in behaviour (eg with respect to imprinting) have led to these cells to be distinguished from one another.

Typically ES/EG cell cultures have well defined characteristics. These include, but are not limited to;

- i) maintenance in culture for at least 20 passages when maintained on fibroblast feeder layers;
- ii) produce clusters of cells in culture referred to as embryoid bodies;
- iii) ability to differentiate into multiple cell types in monolayer culture;
- iv) can form embryo chimeras when mixed with an embryo host;
- v) express ES/EG cell specific markers.

Until very recently, *in vitro* culture of human ES/EG cells was not possible. The first indication that conditions may be determined which could allow the establishment of

human ES/EG cells in culture is described in WO96/22362. The application describes cell lines and growth conditions which allow the continuous proliferation of primate ES cells which exhibit a range of characteristics or markers which are associated with stem cells having pluripotent characteristics.

5

More recently Thomson *et al* (1998) have published conditions in which human ES cells can be established in culture. The above characteristics shown by primate ES cells are also shown by the human ES cell lines. In addition the human cell lines show high levels of telomerase activity, a characteristic of cells which have the ability to divide continuously in culture in an undifferentiated state. Another group (Reubinoff *et. al.*, 2000) have also reported the derivation of human ES cells from human blastocysts. Shambloott *et. al.*, 1998 have also described EG cell derivation. In Lake *et al* J Cell Science 2000, 113:555-66 and Rathjen *et al* J Cell Science 1999, 112: 601-12, ectodermal stem cells are disclosed. The above references are each both

10

15 incorporated by reference in their entirety.

A feature of ES/EG cells is that, in the presence of fibroblast feeder layers, they retain the ability to divide in an undifferentiated state for several generations. If the feeder layers are removed then the cells differentiate. The differentiation is often to neurones or muscle cells but the exact mechanism by which this occurs and its control remain unsolved.

20

In addition to ES/EG cells a number of adult tissues contain cells with stem cell characteristics. Typically these cells, although retaining the ability to differentiate into different cell types, do not have the pluripotential characteristics of ES/EG cells. For example haemopoietic stem cells have the potential to form all the cells of the haemopoietic system (red blood cells, macrophages, basophils, eosinophils etc). All of nerve tissue, skin and muscle retain pools of cells with stem cell potential. Therefore, in addition to the use of embryonic stem cells in developmental biology, there are also adult stem cells which may also have utility with respect to determining the factors which govern cell differentiation. . Further recent studies have suggested

25

30

that some stem cells previously thought to be committed to a single fate, (e.g neurons) may indeed possess considerable pluripotency in certain situations. Neural stem cells have recently been shown to chimerise a mouse embryo and form a wide range of non-neural tissue (Clark et. al., 2000).

5

A further group of cells which have relevance to developmental biology are pluripotent embryonal carcinoma cells (EC cells) which are stem cells of teratocarcinomas, also referred to as teratomas, which are able to differentiate into all cell types found in these tumours. A teratocarcinoma also includes teratocarcinoma cells which do not have the full pluripotential characteristics of an EC cell but nevertheless can differentiate into a restricted number of differentiated tissues. These cells have many features in common with ES/EG cells. The most important of these features is the characteristic of pluripotentiality.

15 Teratomas contain a wide range of differentiated tissues, and have been known in humans for many hundreds of years. They typically occur as gonadal tumours of both men and women. The gonadal forms of these tumours are generally believed to originate from germ cells, and the extra gonadal forms, which typically have the same range of tissues, are thought to arise from germ cells that have migrated incorrectly during embryogenesis. Teratomas are therefore generally classed as germ cell tumours which encompasses a number of different types of cancer. These include
20 seminoma, embryonal carcinoma, yolk sac carcinoma and choriocarcinoma.

The similar biology of EC cells with ES/EG cells has been exploited to study the developmental fates of cells and to identify cell markers commonly expressed in EC
25 cells and ES/EG cells. For example, and not by way of limitation, the expression of specific cell surface markers SSEA-3 (+), SSEA-4 (+), TRA-1-60 (+), TRA-1-81 (+) (Shevinsky *et al* 1982; Kannagi *et al* 1983; Andrews *et al* 1984a; Thomson *et al* 1995); alkaline phosphatase (+) (Andrews et. al., 1996); and Oct 4 (Scholer et. al.,
30 1989; Kraft et. al., 1996; Reubinoff et. al., 2000; Yeom et. al., 1996).

We have accumulated expression studies which identify a number of genes thought to be involved in determining the developmental fate of stem cells, particularly embryonic stem cells. By northern blotting we have identified the expression of human homologs of two signalling pathways believed to be critical in cell fate determination. Expression of ligands, receptors and downstream components of the Notch and Wingless signalling cascades have been elucidated. Using the model system NTERA2/D1 embryonal carcinoma cells we have recorded changes in the expression of some of these components as the cells differentiate. Bearing in mind the role these cascades play in embryonic development throughout the animal kingdom, these changes suggest a significant role for both the wingless and Notch signalling pathways in differentiation of stem cells. Furthermore the activity of some genes are required for differentiation to occur along specific pathways e.g. the myogenic gene MyoD1. Other genes have activity which inhibits cellular differentiation along particular pathways. We envisage regulation of stem cell differentiation to yield a specific cell type could be achieved by:

- (i) inhibition of certain genes that normally promote differentiation along particular pathways; therefore promoting differentiation to alternate cell phenotypes;
- (ii) inhibition of gene activity that prevents differentiation into particular cell types; and
- (iii) a combination of (i) and (ii), see figure 1

In our co-pending application, WO02/16620, we introduce RNAi molecules homologous to genes encoding factors involved in stem cell differentiation. The differentiation of stem cells during embryogenesis, during tissue renewal in the adult and wound repair is under very stringent regulation; aberrations in this regulation underlie the formation of birth defects during development and are thought to underlie cancer formation in adults.

Generally, it is envisaged that stem cells are under both positive and negative regulation which allows a fine degree of control over the process of cell proliferation and cell differentiation: excess proliferation at the expense of cell differentiation can lead to the formation of an expanding mass of tissue – a cancer – whereas express
5 differentiation at the expense of proliferation can lead to the loss of stem cells and production of too little differentiated tissue in the long term, and especially the loss of regenerative potential. Certain genes have already been identified to have a negative role in preventing stem cell differentiation. Such genes, like those of the Notch family, when mutated to acquire activity can inhibit differentiation; such
10 mutant genes act as oncogenes. On the contrary, loss of function of such genes on their inhibition results in stem cell differentiation.

We propose to use EC cells as a model cell system to follow the effects of perturbations in stem cell differentiation. We further propose an alternative approach
15 to introduce double stranded RNA molecules into stem cells to ablate mRNA's.

The invention relates to the provision of stem-loop RNA structures which can either be synthesised *in vitro* followed by transfection into a stem cell, or alternatively, synthesised *in vivo* by the stem cell from vectors which are provided with expression
20 cassettes which include a DNA molecule which includes the coding sequence for the stem-loop RNA.

The DNA molecule encoding the stem-loop RNA is constructed in two parts, a first part which is derived from a gene the regulation of which is desired. The second part
25 is provided with a DNA sequence which is complementary to the sequence of the first part. The cassette is typically under the control of a promoter which transcribes the DNA into RNA. The complementary nature of the first and second parts of the RNA molecule results in base pairing over at least part of the length of the RNA molecule to form a double stranded hairpin RNA structure or stem-loop. The first
30 and second parts can be provided with a linker sequence.

According to a first aspect of the invention there is provided a method to modulate the differentiation state of a stem cell comprising:

- (i) contacting a stem cell with at least one nucleic acid molecule comprising a
5 sequence of a gene which mediates at least one step in the differentiation of said cell which nucleic acid molecule consists of a first part linked to a second part wherein said first and second parts are complementary over at least part of their length and further wherein said first and second parts form a double stranded region by complementary base pairing over at least part of their length;
- 10 (ii) providing conditions conducive to the growth and differentiation of the cell treated in (i) above; and optionally
- (iii) maintaining and/or storing the cell in a differentiated state.

In a preferred method of the invention said first and second parts are linked by at
15 least one nucleotide base.

The provision of first and second sequences which are complementary to one another and which comprise at least part of the coding sequence of a gene involved in stem cell differentiation means that when the sequence is transcribed into RNA the
20 complementarity between first and second sequences allows base pairing between first and second sequences to form a double stranded RNA structure, see Figure 1. The optional provision of a linking region between first and second parts results in the formation of a so called "hair-pin" loop structure. The transcription of the nucleic acid provides many copies of the hair-pin loop RNA which effectively
25 functions as a RNAi molecule.

In a preferred method of the invention said nucleic acid molecule is a stem loop RNA molecule. Alternatively, said nucleic acid molecule is a DNA molecule which encodes said stem loop RNA. Ideally said DNA molecule is a vector adapted for
30 expression of said stem loop RNA.

The stem cell in (i) above may be a teratocarcinoma cell.

In a preferred method of the invention said conditions are *in vitro* cell culture conditions.

5

In a further preferred method of the invention said stem cell is selected from: pluripotent stem cells such as embryonic stem cell; embryonic germ cell and embryonal carcinoma cells; and lineage restricted stem cells such as, but not restricted to; haemopoietic stem cell; muscle stem cell; nerve stem cell; skin dermal sheath stem cell; liver stem cell; and teratocarcinoma cells.

10

It will be apparent that the method can provide stem cells of intermediate commitment. For example, embryonic stem cells could be programmed to differentiate into haemopoietic stems cells with a restricted commitment.

15

Alternatively, differentiated cells or stem cells of intermediate commitment could be reprogrammed to a more pluripotential state from which other differentiated cell lineages can be derived.

In a further preferred method of the invention said stem cell is an embryonic stem cell or embryonic germ cell.

20

In a yet further preferred method of the invention said stem loop RNA molecule is derived from a gene which encodes a cell surface receptor expressed by a stem cell.

In a further preferred method of the invention said cell surface receptor is selected from: human Notch 1(hNotch 1); hNotch 2; hNotch 3; hNotch 4; TLE-1; TLE-2; TLE-3; TLE-4; TCF7; TCF7L1; TCF7L2; TCF3; TCF19; TCF1; mFringe; lFringe; rFringe; sel 1; Numb; Numblake; LNX; FZD1; FZD2; FZD3; FZD4; FZD5; FZD6; FZD7; FZD8; FZD9; FZD10; FRZB.

25

30

In an alternative preferred method of the invention said stem loop RNA molecule is derived from a gene which encodes a ligand.

Typically, a ligand is a polypeptide which binds to a cognate receptor to induce or
5 inhibit an intracellular or intercellular response. Ligands may be soluble or membrane bound.

In a further alternative preferred method of the invention said ligand is selected from:
D11-1; D113; D114; D1k-1; Jagged 1; Jagged 2; Wnt 1; Wnt 2; Wnt 2b; Wnt 3; Wnt
10 3a; Wnt5a; Wnt6; Wnt7a; Wnt7b; Wnt8a; Wnt8b; Wnt10b; Wnt11; Wnt14; Wnt15.

Alternatively, said gene is selected from: SFRP1; SFRP2; SFRP4; SFRP5; SK;
DKK3; CER1; WIF-1; DVL1; DVL2; DVL3; DVL1L1;mFringe; lFringe; rFringe;
sel11; Numb; LNX Oct4; NeuroD1; NeuroD2; NeuroD3; Brachyury; MDFl.
15

In a further preferred method of the invention said stem loop RNA molecule is derived from at least one of the sequences identified in Table 4 or Figures 4-54.

In a yet further preferred embodiment of the invention said sequence is derived from
20 Oct 4. Preferably the Oct 4 sequence corresponds to nucleotide sequence about 610 to about 1032 of the Oct 4 sequence found in GenBank accession number NM_002701.

Many methods have been developed over the last 30 years to facilitate the
25 introduction of nucleic acid into cells which are well known in the art and are applicable to the stem loop RNA structures disclosed herein or the vectors which encode said stem loop structures.

Methods to introduce nucleic acid into cells typically involve the use of chemical
30 reagents, cationic lipids or physical methods. Chemical methods which facilitate the uptake of DNA by cells include the use of DEAE -Dextran (Vaheri and Pagano Science 175: p434) . DEAE-dextran is a negatively charged cation which associates

and introduces the nucleic acid into cells. Calcium phosphate is also a commonly used chemical agent which when co-precipitated with nucleic acid introduces the nucleic acid into cells (Graham et al Virology (1973) 52: p456).

5 The use of cationic lipids (eg liposomes (Felgner (1987) Proc.Natl.Acad.Sci USA, 84:p7413) has become a common method. The cationic head of the lipid associates with the negatively charged nucleic acid backbone to be introduced. The lipid/nucleic acid complex associates with the cell membrane and fuses with the cell to introduce the associated nucleic acid into the cell. Liposome mediated nucleic acid transfer has
10 several advantages over existing methods. For example, cells which are recalcitrant to traditional chemical methods are more easily transfected using liposome mediated transfer.

More recently still, physical methods to introduce nucleic acid have become effective
15 means to reproducibly transfect cells. Direct microinjection is one such method which can deliver nucleic acid directly to the nucleus of a cell (Capecchi (1980) Cell, 22:p479). This allows the analysis of single cell transfectants. So called "biolistic" methods physically shoot nucleic acid into cells and/or organelles using a particle gun (Neumann (1982) EMBO J, 1: p841). Electroporation is arguably the
20 most popular method to transfect nucleic acid. The method involves the use of a high voltage electrical charge to momentarily permeabilise cell membranes making them permeable to macromolecular complexes.

More recently still a method termed immunoporation has become a recognised
25 technique for the introduction of nucleic acid into cells, see Bildirici *et al* Nature (2000) 405, p298. The technique involves the use of beads coated with an antibody to a specific receptor. The transfection mixture includes nucleic acid, antibody coated beads and cells expressing a specific cell surface receptor. The coated beads bind the cell surface receptor and when a shear force is applied to the cells the beads are
30 stripped from the cell surface. During bead removal a transient hole is created through which nucleic acid and/or other biological molecules can enter. Transfection

efficiency of between 40-50% is achievable depending on the nucleic acid used. In addition the specificity of cell delivery of RNAi's can be enhanced by association or linkage of the RNAi to specific antibodies, ligands or receptors.

- 5 There are also a number of commercially available transfection kits which purport to provide high efficiency transfection of cells. A kit which is particularly preferred is sold under the tradename ExGen 500tm by MBI Fermentas, Lithuania. ExGen is a polyethylenimine, non-liposomal transfection reagent.
- 10 According to a further aspect of the invention there is provided a stem loop RNA molecule derived from a coding sequence of at least one gene involved in stem cell differentiation comprising a first part linked to a second part wherein said first and second parts are complementary over at least part of their length and further wherein said first and second parts form a double stranded region by complementary base
- 15 pairing over at least part of their length.

In a preferred embodiment of the invention said first and second parts are linked by at least one nucleotide base. In a further preferred embodiment of the invention said first and second parts are linked by 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide bases. In a

20 yet further preferred embodiment of the invention said linker is at least 10 nucleotide bases.

In a preferred embodiment said coding sequence is an exon.

- 25 Alternatively said RNA molecule is derived from intronic sequences or the 5' and/or 3' non-coding sequences which flank coding/exon sequences of genes which mediate stem cell differentiation.

In a further preferred embodiment of the invention the length of the RNA molecule is

30 between 10 nucleotide bases (nb) –1000nb. More preferably still the length of the

RNA molecule is selected from 10nb; 20nb; 30nb; 40nb; 50nb; 60nb; 70nb; 80nb; 90nb. More preferably still said RNA molecule is 21nb in length.

In a further preferred embodiment of the invention said RNA molecule is 100nb;
5 200nb; 300nb; 400nb; 500nb; 600nb; 700nb; 800nb; 900nb; or 1000nb. More preferably still said RNA molecule is at least 1000nb.

In a further preferred embodiment of the invention said RNA molecule comprises sequences identified in Table 4 or Figures 4-54.

10

In yet a further preferred embodiment of the invention said RNA molecules comprise modified nucleotide bases.

It will be apparent to one skilled in the art that the inclusion of modified bases, as
15 well as the naturally occurring bases cytosine, uracil, adenosine and guanosine, may confer advantageous properties on RNA molecules containing said modified bases. For example, modified bases may increase the stability of the RNA molecule thereby reducing the amount required to produce a desired effect. The provision of modified bases may also provide stem-loop structures which are more or less stable.

20

According to a further aspect of the invention there is provided a nucleic acid molecule encoding at least part of a gene which mediates at least one step in stem cell differentiation comprising a first part linked to a second part which first and second parts are complementary over at least part of their length, wherein said nucleic acid
25 molecule is operably linked to at least one further nucleic acid molecule capable of promoting transcription of said nucleic acid linked thereto and further wherein said first and second parts form a double stranded region by complementary base pairing over at least part of their length as or when said nucleic acid molecule is transcribed.

30 In a preferred embodiment of the invention said first and second parts are linked by linking nucleotides as hereinbefore described.

It will be apparent to one skilled in the art that the synthesis of RNA molecules which form RNA stem loops can be achieved by providing vectors which include target genes, or fragments of target genes, operably linked to promoter sequences.

5 Typically, promoter sequences are phage RNA polymerase promoters (eg T7, T3, SP6). Advantageously vectors are provided with multiple cloning sites into which genes or gene fragments can be subcloned. Typically, vectors are engineered so that phage promoters flank multiple cloning sites containing the gene of interest.

10 Alternatively target genes or fragments of target genes can be fused directly to phage promoters by creating chimeric promoter/gene fusions via oligo synthesising technology. Constructs thus created can be easily amplified by polymerase chain reaction to provide templates for the manufacture of RNA molecules comprising stem loop RNA's.

15

According to a further aspect of the invention there is provided a vector including an expression cassette comprising a first sequence linked to a second sequence wherein said first and second sequences are complementary over at least part of their lengths and further wherein the expression cassette is transcriptionally linked to a promoter
20 sequence.

In a preferred embodiment of the invention said first and second parts are linked by linking nucleotides as hereinbefore described.

25 Vectors including expression cassettes encoding stem-loop RNA's are adapted for eukaryotic gene expression. Typically said adaptation includes, by example and not by way of limitation, the provision of transcription control sequences (promoter sequences) which mediate cell/tissue specific expression. These promoter sequences may be cell/tissue specific, inducible or constitutive.

30

Promoter elements typically also include so called TATA box and RNA polymerase initiation selection sequences which function to select a site of transcription initiation. These sequences also bind polypeptides which function, *inter alia*, to facilitate transcription initiation selection by RNA polymerase.

5

Adaptations also include the provision of selectable markers and autonomous replication sequences which both facilitate the maintenance of said vector in either the eukaryotic cell or prokaryotic host. Vectors which are maintained autonomously are referred to as episomal vectors. Further adaptations which facilitate the expression of vector encoded genes include the provision of transcription termination sequences.

These adaptations are well known in the art. There is a significant amount of published literature with respect to expression vector construction and recombinant DNA techniques in general. Please see, Sambrook et al (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbour Laboratory, Cold Spring Harbour, NY and references therein; Marston, F (1987) DNA Cloning Techniques: A Practical Approach Vol III IRL Press, Oxford UK; DNA Cloning: F M Ausubel et al, Current Protocols in Molecular Biology, John Wiley & Sons, Inc.(1994).

20

According to a further aspect of the invention there is provided a cell transfected with the nucleic acid or vector according to the invention. Preferably said cell is an embryonic stem cell or embryonic germ cell. Alternatively said cell is an embryonal carcinoma cell.

25

According to a further aspect of the invention there is provided a method to manufacture stem loop RNA molecules comprising:

- (i) providing a vector or promoter/gene fusion according to the invention;

30

(ii) providing reagents and conditions which allow the synthesis of the RNA molecule comprising a stem loop RNA molecule according to the invention; and

(iii) providing conditions which allow the RNA molecule to base pair over at least
5 part of its length, or at least that part corresponding to the nucleic acid sequence encoding said stem cell gene which mediates stem cell differentiation.

Preferably said gene, or gene fragment is selected from those genes represented in table 4 or Figures 4-54.

10

In vitro transcription of RNA is an established methodology. Kits are commercially available which provide vectors, ribonucleoside triphosphates, buffers, Rnase inhibitors, RNA polymerases (eg phage T7, T3, SP6) which facilitate the production of RNA.

15

According to a further aspect of the invention there is provided an *in vivo* method to promote the differentiation of stem cells comprising administering to an animal an effective amount of stem loop RNA molecule, or vector encoding a stem loop RNA molecule according to the invention, sufficient to effect differentiation of a target
20 stem cell.

Preferably said method promotes differentiation *in vivo* of endogenous stem cells to repair tissue damage *in situ*.

25 It will be apparent to one skilled in the art that stem loop RNA relies on homology between the target gene RNA and double stranded region of the stem loop in a similar way to conventional RNAi. This confers a significant degree of specificity to the stem loop RNA molecule in targeting stem cells. For example, haemopoietic stem cells are found in bone marrow and stem loop RNA molecules may be
30 administered to an animal by direct injection into bone marrow tissue.

Stem loop RNA molecules may be encapsulated in liposomes to provide protection from an animals immune system and/or nucleases present in an animals serum.

5 Liposomes are lipid based vesicles which encapsulate a selected therapeutic agent which is then introduced into a patient. Typically, the liposome is manufactured either from pure phospholipid or a mixture of phospholipid and phosphoglyceride. Typically liposomes can be manufactured with diameters of less than 200nm, this enables them to be intravenously injected and able to pass through the pulmonary capillary bed. Furthermore the biochemical nature of liposomes confers
10 permeability across blood vessel membranes to gain access to selected tissues. Liposomes do have a relatively short half-life. So called STEALTH^R liposomes have been developed which comprise liposomes coated in polyethylene glycol (PEG). The PEG treated liposomes have a significantly increased half-life when administered intravenously to a patient. In addition STEALTH^R liposomes show reduced uptake
15 in the reticuloendothelial system and enhanced accumulation selected tissues. In addition, so called immuno-liposomes have been develop which combine lipid based vesicles with an antibody or antibodies, to increase the specificity of the delivery of the RNAi molecule to a selected cell/tissue.

20 The use of liposomes as delivery means is described in US5580575 and US 5542935.

It will be apparent to one skilled in the art that the stem loop RNA molecules can be provided in the form of an oral or nasal spray, an aerosol, suspension, emulsion, and/or eye drop fluid. Alternatively the stem loop RNA molecules may be provided in tablet form. Alternative delivery means include inhalers or nebulisers.

25

According to a yet further aspect of the invention there is provided a therapeutic composition comprising a stem loop RNA molecule according to the invention or a vector encoding a stem loop RNA according to the invention.

30 Preferably said stem loop RNA molecule or vector is for use in the manufacture of a medicament for use in promoting the differentiation of stem cells to provide

differentiated cells/tissues to treat diseases where cell/tissues are destroyed by said disease.

Typically this includes pernicious anemia; stroke, neurodegenerative diseases such as
5 Parkinson's disease, Alzheimer's disease; coronary heart disease; cirrhosis;
diabetes. It will also be apparent that differentiated stem cells may be used to replace
nerves damaged as a consequence of (eg replacement of spinal cord tissue).

In a further preferred embodiment of the invention said therapeutic composition
10 further comprises a diluent, carrier or excipient.

According to a further aspect of the invention there is provided a cell obtainable by
the method according to the invention.

15 It will be apparent that a cell obtainable by the method according to the invention has
useful applications. For example, a stably transfected cell under the control of a
regulatable promoter (ie inducible, repressible, developmentally regulated, cell
lineage regulated, cell-cycle regulated) offers the opportunity to modulate the
expression of the stem-loop RNA in said cell thereby modulating the differentiation
20 state, or not as the case maybe, in culture or *in vivo*.

According to a yet further aspect of the invention there is provided at least one organ
comprising at least one cell obtainable by the method according to the invention.

25 According to a yet further aspect of the invention there is provided a non-human
transgenic animal comprising a RNA molecule according to the invention, or a
nucleic acid molecule according to the invention, or a vector according to the
invention.

30 An embodiment of the invention will now be described by example only and with
reference to the following figures and tables wherein:

Table 1 represents a selection of antibodies used to monitor stem cell differentiation;

Table 2 represents nucleic acid probes used to assess mRNA markers of stem
5 differentiation;

Table 3 represents protein markers of stem cell differentiation;

10 Table 4 represents specific primers used to generate stem loop RNA for gene
specific inhibition;

Table 5 represents vectors used for the expression of stem loop RNA in cells
including the promoters used to drive transcription of stem loop RNA's.

15

Figure 1 illustrates stem cell differentiation is controlled by positive and negative
regulators (A). The specific cell phenotypes that are derived are a direct result of
positive and negative regulators which activate or suppress particular differentiation
events. Stem loop RNA can be used to control both the initial differentiation of stem
20 cells (A) and the ultimate fate of the differentiated cells D1 and D2 by repression of
positive activators which would normally promote a particular cell fate;

Figure 2 represents the Oct 4 nucleic acid sequence from position 610-1032 of the
sequence found in GenBank accession number NM_002701.

25

Fig 3A illustrates a transcription cassette comprising a promoter sequence operable
linked to a nucleic acid encoding a stem loop RNA; Fig 3B illustrates a stem loop
RNA synthesised from the cassette illustrated in Fig 1A;

30 Figure 4 is the nucleic acid sequence of murine notch ligand delta-like 1;

Figure 5 is the nucleic acid sequence of murine notch ligand jagged 1;

Figure 6 is the nucleic acid sequence of human notch ligand jagged 1 (alagille syndrome) (JAG1);

Figure 7 is the nucleic acid sequence of human notch ligand jagged 2 (JAG2)

5

Figure 8 is the nucleic acid sequence of murine notch ligand jagged 2;

Figure 9 is the nucleic acid sequence of human notch ligand delta-like 3 (DLL3);

10 Figure 10 is the nucleic acid sequence of human notch ligand delta-1 (DLL1);

Figure 11 is the nucleic acid sequence of human notch ligand delta-like 4 (DLL4);

Figure 12 is the nucleic acid sequence of murine notch ligand delta-like 4 (DLL4);

15

Figure 13 represents the nucleic acid sequence of human *Wnt 13*;

Figure 14 represents the nucleic acid sequence of human *dickkopf1*;

20 Figure 15 represents the nucleic acid sequence of human *dickkopf2*;

Figure 16 represents the nucleic acid sequence of human *dickkopf3*; and

Figure 17 represents the nucleic acid sequence of human *dickkopf4*;

25

Figure 18 represents the nucleic acid sequence of WNT-1;

Figure 19 represents the nucleic acid sequence of WNT-2;

30 Figure 20 represents the nucleic acid sequence of WNT 2B;

Figure 21 represents the nucleic acid sequence of WNT 3;

Figure 22 represents the nucleic acid sequence of WNT 4;

5 Figure 23 represents the nucleic acid sequence of WNT 5A;

Figure 24 represents the nucleic acid sequence of WNT 6;

Figure 25 represents the nucleic acid sequence of WNT 7A;

10

Figure 26 represents the nucleic acid sequence of WNT 8B;

Figure 27 represents the nucleic acid sequence of WNT 10B;

15 Figure 28 represents the nucleic acid sequence of WNT 11;

Figure 29 represents the nucleic acid sequence of WNT 14

Figure 30 represents the nucleic acid sequence of WNT 16;

20

Figure 31 represents the nucleic acid sequence of FZD 1;

Figure 32 represents the nucleic acid sequence of FZD 2;

25 Figure 33 represents the nucleic acid sequence of FZE 3;

Figure 34 represents the nucleic acid sequence of FZD 4;

Figure 35 represents the nucleic acid sequence of FZD 5;

30

Figure 36 represents the nucleic acid sequence of FZD 6;

Figure 37 represents the nucleic acid sequence of FZD 7;

Figure 38 represents the nucleic acid sequence of FZD 8;

5

Figure 39 represents the nucleic acid sequence of FZD 9;

Figure 40 represents the nucleic acid sequence of FZD 10;

10 Figure 41 represents the nucleic acid sequence of FRP;

Figure 42 represents the nucleic acid sequence of SARP 1;

Figure 43 represents the nucleic acid sequence of SARP 2;

15

Figure 44 represents the nucleic acid sequence of FRZB;

Figure 45 represents the nucleic acid sequence of FRPHE;

20 Figure 46 represents the nucleic acid sequence of SARP 3;

Figure 47 represents the nucleic acid sequence of CER 1;

Figure 48 represents the nucleic acid sequence of DKK1;

25

Figure 49 represents the nucleic acid sequence of DKK 2;

Figure 50 represents the nucleic acid sequence of DKK 3;

30 Figure 51 represents the nucleic acid sequence of DKK 4;

Figure 52 represents the nucleic acid sequence of WIF-1;

Figure 53 represents the nucleic acid sequence of SRFP 1;

5 Figure 54 represents the nucleic acid sequence of SRFP 4;

10

15 Materials and Methods

Cell Culture

NTERA2 and 2102Ep human EC cell lines were maintained at high cell density as previously described (Andrews et al 1982, 1984b), in DMEM (high glucose
20 formulation) (DMEM)(GIBCO BRL), supplemented with 10% v/v bovine foetal calf serum (GIBCO BRL), under a humidified atmosphere with 10% CO₂ in air.

Stem Loop RNA Production

25 Primers were designed against specific target genes with T7 bacteriophage promoters at their 5' ends . The primers consist of typically 18- 25 bp against the target gene, a linker sequence of variable length (indicated by N in primer sequence) followed by the reverse complement of the gene specific sequence. The primers were used in a standard RNA in vitro. transcription reaction using a MEGASCRIP^T kit following
30 manufacturers protocols (Ambion, USA). Longer siRNA templates were produced by cloning head-to -tail the sense and anti-sense gene specific sequences to generate a palindromic template from which RNA could be synthesized.

The following primers were used
35

Gene	Accession Number	Primer Sequence
Oct4	Z11899	TAA TAC GAC TCA CTA TAG Ggagcagctfgggctcgagaag(N)cttctcgagcccaagctgctc
HsNotch2		TAA TAC GAC TCA CTA TAGGt cgt gca aga gcc agt tac cc(N)gg gta act ggc tct tgcacg a
HsNotch1	M73980	TAA TAC GAC TCA CTA TAGGa atg gtc aat gcg agt ggc tgt cc(N)gg aca gcc act cgc gtt gac cat t
CIF		TAA TAC GAC TCA CTA TAGGa gta gtg aga gtg aga gta aca(N)tgt tac tct cac tct cac tac t
RBPJ-kappa		TAA TAC GAC TCA CTA TAGGt cctgtg cctgtg gta gag a(N)t ctc tac cac agg cac agg a
Dlk1	NM_002226	TAA TAC GAC TCA CTA TAGGcctc ttg ctc ctg ctg gct tt(N)aaagccagcaggagcaagagg

Capital letters indicate the T7 polymerase promoter sequence.

- 5 In each case, a quantity of the PCR was electrophoresed through agarose to verify product size and abundance, whilst the remainder was purified by alkaline phenol/chloroform extraction. RNA was synthesized using the Megascript kit (Ambion Inc.) according to the manufacturer's protocol and acid phenol/chloroform extracted. The simultaneous synthesis of complementary strands of RNA in a single
- 10 reaction circumvents the requirement for an annealing step. However, the quality and duplexing of the synthesized RNA was confirmed by agarose gel electrophoresis, with the desired products migrating as expected for double stranded DNA of the same length.

15 Stem Loop RNA introduction to Cell Lines

Human EC stem cells were seeded at 2×10^5 cells/well of a 6 well plate in 3 cm^3 of Dulbecco's modified Eagles medium and allowed to settle for 3 hrs.

- Appx. $9.5 \mu\text{g}$ of DNA was incubated with an optimised amount of ExGEN 500 for
- 20 each well of a 6-well plate. Previously cells were seeded 1 day before. This gives apprx. a 70% confluent culture. The DNA/ExGen mixture was added to the cells and the culture vessel spun at 280g for 5 mins.

Total RNA production

Growing cultures of cells were aspirated to remove the DME and foetal calf serum. Trace amounts of foetal calf serum was removed by washing in Phosphate-buffered saline. Fresh PBS was added to the cells and the cells were dislodged from the culture vessel using acid washed glass beads. The resulting cell suspension was centrifuged at 300xg. The pellets had the PBS aspirated from them. Tri reagent (Sigma, USA) was added at 1ml per 10^7 cells and allowed to stand for 10 mins at room temperature. The lysate from this reaction was centrifuged at 12000 x g for 15 minutes at 4°C. The resulting aqueous phase was transferred to a fresh vessel and 0.5 ml of isopropanol / ml of trizol was added to precipitate the RNA. The RNA was pelleted by centrifugation at 12000 x g for 10 mins at 4°C. The supernatant was removed and the pellet washed in 70% ethanol. The washed RNA was dissolved in DEPC treated double-distilled water.

Analysis of the differentiation of EC stem cells induced by exposure to Stem Loop RNA

Following exposure to stem loop RNA corresponding to specific key regulatory genes, the subsequent differentiation of the EC cells was monitored in a variety of ways. One approach was to monitor the disappearance of typical markers of the stem cell phenotype; the other was to monitor the appearance of markers pertinent to the specific lineages induced. The relevant markers included surface antigens, mRNA species and specific proteins.

Analysis of Transfectants by Antibody Staining and FACS

Cells were treated with trypsin (0.25% v/v) for 5 mins to disaggregate the cells; they were washed and re-suspended to 2×10^5 cells/ml. This cell suspension was incubated with 50µl of primary antibody in a 96 well plate on a rotary shaker for 1 hour at 4°C. Supernatant from a myeloma cell line P3X63Ag8, was used as a negative control. The 96 well plate was centrifuged at 100rpm for 3 minutes. The plate was washed 3 times with PBS containing 5% foetal calf serum to remove unbound antibody. Cell

were then incubated with 50 µl of an appropriate FITC-conjugated secondary antibody at 4°C for 1 hour. Cells were washed 3 times in PBS + 5% foetal calf serum and analysed using an EPICS elite ESP flow cytometer (Coulter electronics, U.K.).(Andrews et. al., 1982)

5

Northern blot Analysis of RNA

RNA separation relies on the generally the same principles as standard DNA but with some concessions to the tendency of RNA to hybridise with itself or other RNA molecules. Formaldehyde is used in the gel matrix to react with the amine groups of the RNA and form Schiff bases. Purified RNA is run out using standard agarose gel electrophoresis. For most RNA a 1% agarose gel is sufficient. The agarose is made in 1X MOPS buffer and supplemented with 0.66M formaldehyde. Dried down RNA samples are reconstituted and denatured in RNA loading buffer and loaded into the gel. Gels are run out for approx. 3 hrs (until the dye front is 3/4 of the way down the gel).

15

The major problem with obtaining clean blotting using RNA is the presence of formaldehyde. The run out gel was soaked in distilled water for 20 mins with 4 changes, to remove the formaldehyde from the matrix. The transfer assembly was assembled in exactly the same fashion as for DNA (Southern) blotting. The transfer buffer used however was 10X SSPE. Gels were transferred overnight. The membrane was soaked in 2X SSPE to remove any agarose from the transfer assembly and the RNA was fixed to the membrane. Fixation was achieved using short-wave (254 nm) UV light. The fixed membrane was baked for 1-2 hrs to drive off any residual formaldehyde.

25

Hybridisation was achieved in aqueous phase with formamide to lower the hybridisation temperatures for a given probe. RNA blots were prehybridised for 2-4 hrs in northern prehybridisation solution. Labelled DNA probes were denatured at 95°C for 5 mins and added to the blots. All hybridisation steps were carried out in rolling bottles in incubation ovens. Probes were hybridised overnight for at least 16

30

hrs in the prehybridisation solution. A standard set of wash solutions were used. Stringency of washing was achieved by the use of lower salt containing wash buffers. The following wash procedure is outlined as follows

	2X SSPE	15 mins	room temp
5	2X SSPE	15 mins	room temp
	2X SSPE/ 0.1% SDS	45 mins	65°C
	2X SSPE/ 0.1% SDS	45 mins	65°C
	0.1X SSPE	15 mins	room temp

10 Preparation of radiolabelled DNA probes

The method of Feinberg and Vogelstein (Feinberg and Vogelstein, 1983) was used to radioactively label DNA. Briefly, the protocol uses random sequence hexanucleotides to prime DNA synthesis at numerous sites on a denatured DNA template using the

15 Klenow DNA polymerase I fragment. Pre-formed kits were used to aid consistency . 5-100ng DNA fragment (obtained from gel purification of PCR or restriction digests) was made up in water, denatured for 5 mins at 95°C with the random hexamers. The mixture was quenched cooled on ice and the following were added,

- 5 µl [α -³²P] dATP 3000 Ci/mmol
- 20 1 µl of Klenow DNA polymerase (4U)
- The reaction was then incubated at 37°C for 1 hr. Unincorporated nucleotides were removed with spin columns (Nucleon Biosciences).

Production of cDNA

25 The enzymatic conversion of RNA into single stranded cDNA was achieved using the 3' to 5' polymerase activity of recombinant Moloney-Murine Leukemia Virus (M-MLV) reverse transcriptase primed with oligo (dT) and (dN) primers. For Reverse Transcription-Polymerase Chain Reaction, single stranded cDNA was used.

30 cDNA was synthesised from 1µg poly (A)+ RNA or total RNA was incubated with the following

1.0µM oligo(dT) primer for total RNA or random hexamers for mRNA

0.5mM 10mM dNTP mix
1U/ μ l RNase inhibitor (Promega)
1.0U/ μ l M-MLV reverse transcriptase in manufacturers supplied buffer
(Promega)

- 5 The reaction was incubated for 2-3 hours at 42°C

Fluorescent Automated Sequencing

To check the specificity of the PCR primers used to generate the template used in stem loop RNA production automatic sequencing was carried out using the prism
10 fluorescently labelled chain terminator sequencing kit (Perkin-Elmer) (Prober et al 1987). A suitable amount of template (200ng plasmid, 100ng PCR product), 10 μ M sequencing primer (typically a 20mer with 50% G-C content) were added to 8 μ l of prism pre-mix and the total reaction volume made up to 20 μ l. 24 cycles of PCR (94°C for 10 seconds, 50°C for 10 seconds, 60°C for 4 minutes). Following thermal
15 cycling, products were precipitated by the addition of 2 μ l of 3M sodium acetate and 50 μ l of 100 % ethanol. DNA was pelleted in an Eppendorf microcentrifuge at 13000 rpm, washed once in 70% ethanol and vacuum dried. Samples were analysed by the in-house sequencing Service (Krebs Institute). Dried down samples were resuspended in 4 μ l of formamide loading buffer, denatured and loaded onto a ABI
20 373 automatic sequencer. Raw sequence was collected and analysed using the ABI prism software and the results were supplied in the form of analysed histogram traces.

Detection of specific protein targets by SDS-PAGE and Western Blotting

25 To obtain cell lysates monolayers of cells were rinsed 3 times with ice-cold PBS supplemented with 2 mM CaCl₂. Cells were incubated with 1 ml/75 cm² flask lysis buffer (1% v/v NP40, 1% v/v DOC, 0.1 mM PMSF in PBS) for 15 min at 4°C. Cell lysates were transferred to eppendorf tubes and passed through a 21 gauge needle to
30 shear the DNA. This was followed by freeze thawing and subsequent centrifugation (30 min, 4°C, 15000g) to remove insoluble material. Protein concentrations of the

supernatants were determined using a commercial protein assay (Biorad). Samples were prepared for SDS-PAGE by adding 6 times Laemmli electrophoresis sample buffer and boiling for 5 min. After electrophoresis with 16 µg of protein on a 10% polyacrylamide gel (Laemmli, 1970) the proteins were transferred to PVDF membrane. The blots were washed with PBS and 0.05% Tween (PBS-T). Blocking of the blots occurred in 5% milk powder in PBS-T (60 min, at RT). Blots were incubated with the appropriate primary antibody. Horseradish peroxidase labelled secondary antibody was used to visualise antibody binding by ECL (Amersham, Bucks., UK). Materials used for SDS-PAGE and western blotting were obtained from Biorad (California, USA) unless stated otherwise.

Table 1: Antibodies used to detect stem cell differentiation

Antibody	Class	Species	Cell phenotype detected	Changes on Differentiation	Reference
TRA-1-60	IgM	Mouse	Human EC, ES cells.	↓ differentiation	Andrews et.al., 1984a
TRA-1-81	IgM	Mouse	Human EC, ES cells.	↓ differentiation	Andrews et. al., 1984a
SSEA3	IgM	Rat	Human EC, ES cells.	↓ differentiation	Shevinsky et al 1982, Fenderson et al 1987
SSEA4	IgG	Mouse	Human EC, ES cells.	↓ differentiation	Kannagi et al 1983 Fenderson et al 1987
A2B5	IgM	Mouse		↑ differentiation	Fenderson et al 1987
ME311	IgG	Mouse		↑ differentiation	Fenderson et al 1987
VIN-IS-56	IgM	Mouse		↑ differentiation	Andrews et al 1990
VIN-IS-53	IgG	Mouse		↑ differentiation	Andrews et al 1990

15

Table 2: Probes used to assess mRNA markers of differentiation

Gene	Cell Type
Synaptophysin	Neuron
NeuroD1	Neuron
MyoD1	Muscle
Collagens	Cartilage
Alpha-actin	Skeletal muscle
Smooth-muscle actin	Smooth muscle

5

10

Table 3: Protein markers of differentiation, detected by Western Blot and/or immunofluorescence.

15 The following antibodies were detected by the appropriate commercially available antibodies

Cell Type	Antigen
Neurons	Neurofilaments
Glial cells	GFAP
Epithelial cells	Cytokeratins
Mesenchymal cells	Vimentin
Muscle	Desmin
Muscle	Tissue specific actins
Connective tissue cells	Collagens

Table 4: Specific Primers used to generate Stem Loop RNA for gene specific inhibition

5 All sequences written 5' to 3'

	Gene Name	Accession number	PCR primer Sequences	Position
Notch Pathway				
Ligands:				
	Dll-1	AF003522		
	Dll3	NM_016941		
	Dll4	NM_019454		
	Dlk-1	NM_003836		
	Jagged1	U73936		
	Jagged2	NM_002226		
Receptors:				
	Notch1	M73980	gcggccgccttgtggttctgttc gccggcgcgtcctcctcttcc	5224-5726
	Notch2	In-house sequence	gccagaatgatgctacctgt tagagcagcaccaatggaac	
	Notch3	U97669	Aagttacccccaagaggcaagtgt Aaggaaatgagaggccagaagga ga	7013-7348
	Notch4	U95299	ggctgccctcccactctcg cagcccgggccccaggatag	3727-4132
Downstream:				
	TLE-1	NM_005077		
	TLE-2	M99436		
	TLE-3	M99438		
	TLE-4	M99439		

	TCF7	NM_003202		
	TCF7L2	Y11306		
	TCF3	M31523		
	TCF19	NM_007109		
	TCF1	NM_000545		
	mfringe	NM_002405		
	lfringe	U94354		
	rFringe	AF108139		
	Sell	AF157516		
	Numb	NM_003744		
	LNK	NM_010727		
Wingless Pathway				
Ligands				
	Wnt1	NM_005430		
	Wnt2	NM_003391		
	Wnt2B	NM_004185	tgagtgggtcctgtactctg actcacactgggtaacacgg	1159-1503
	Wnt5A	L20861		
	Wnt6	AF079522		
	Wnt7A	NM_004625		
	Wnt8B	NM_003393		
	Wnt10B	NM_003394		
	Wnt11	NM_004626		
	Wnt14	AF028702		
	Wnt15	AF028703		
	Wnt16	AF169963		
Receptors				
	FZD1	NM_003505		
	FZD2	NM_001466	taccagagcggtatcatctttt	955-1439

			acgaagccggccaggaggaaggac	
	FZD3	NM_017412		
	FZD4	NM_012193		
	FZD5	NM_003468		
	FZD6	NM_003506	Tggcctgaggagcttgaatgtgac Atgcccagcaaaaatccaatgaa	607-1026
	FZD7	NM_003507		
	FZD8	AA481448		
	FZD9	NM_003508		
	FZD10	NM_007197		
	FRZB	NM_001463		
Extracellular Effectors				
	SFRP1	NM_003012		
	SFRP2	AF017986		
	SFRP4	AF026692	agaggagtggctgcaatgaggtc gcgcccggctgttttctt	877-1178
	SFRP5	NM_003015		
	SK	AB020315		
	CER1	NM_005454		
	WIF-1	NM_007191		
	DVL1	U46461		
	DVL2	NM_004422		
	DVL3	NM_004423		
Transcription Factors				
	Oct4	Z11899		
	Brachyury	NM_003181		

	NeuroD1	NM_002500		
	NeuroD2	NM_006160		
	NeuroD3	U63842		
	MyoD	NM_002478		
	MDFI	NM_005586		
	REST	NM_005612		

Table 5

- 5 Listed are examples of vector systems that are to be used in cells to direct the production of stem loop RNA.

Expression System	Vectors	Accession numbers	Promoters
Tet-on/Tet-off Clontech, USA	pTet-on pTet-off pTRE2-Hyg	U89930 U89929	CMV MyoD1 NeuroD1 Oct4 GATA1 Beta-actin PGK
IRES Invitrogen, Netherlands)	pIRES-EGFP		CMV MyoD1 NeuroD1 Oct4 GATA1 Beta-actin PGK
Ecdysone Invitrogen, Netherlands	pIND pVgRXR		CMV MyoD1 NeuroD1 Oct4 GATA1 Beta-actin PGK

References

5

Andrews P.W., Goodfellow P.N., Shevinsky L., Bronson D. L. and Knowles B.B. 1982. Cell surface antigens of a clonal human embryonal carcinoma cell line: Morphological and antigenic differentiation in culture. *Int. J. Cancer*. 29: 523-531.

10 Andrews P.W., Banting G.S., Damjanov I., Arnaud D. and Avner P. 1984a. Three monoclonal antibodies defining distinct differentiation antigens associated with different high molecular weight polypeptides on the surface of human embryonal carcinoma cells. *Hybridoma*. 3: 347-361.

15 Andrews P.W., Damjanov I., Simon D., Banting G., Carlin C., Dracopoli N.C. and Fogh J. 1984b. Pluripotent embryonal carcinoma clones derived from the human teratocarcinoma cell line Tera-2: Differentiation *in vivo* and *in vitro*. *Lab. Invest*. 50: 147-162.

20 Andrews P.W., Nudelman E., Hakomori S. -i. and Fenderson B.A. 1990. Different patterns of glycolipid antigens are expressed following differentiation of TERA-2 human embryonal carcinoma cells induced by retinoic acid, hexamethylene bisacetamide (HMBA) or bromodeoxyuridine (BUdR). *Differentiation*. 43: 131-138.

25 Fenderson B.A., Andrews P.W., Nudelman E., Clausen H. and Hakomori S.-i. 1987. Glycolipid core structure switching from globo- to lacto- and ganglio-series during retinoic acid-induced differentiation of TERA-2-derived human embryonal carcinoma cells. *Dev. Biol*. 122: 21-34.

30 Kannagi, R., Levery, S.B., Ishigami, F., Hakomori, S., Shevinsky, L.H., Knowles, B.B. and Solter, D. (1983) New globoseries glycosphingolipids in human teratocarcinoma reactive with the monoclonal antibody directed to a developmentally regulated antigen, stage-specific embryonic antigen 3. *J. Biol. Chem*. 258, 8934-8942.

- Shevinsky, L.H., Knowles, B.B., Damjanov, I. and Solter, D. (1982) Monoclonal antibody to murine embryos defines a stage-specific embryonic antigen expressed on mouse embryos and human teratocarcinoma cells. *Cell* 30, 697-705.
- Solter, D. and Knowles, B.B. (1978) Monoclonal antibody defining a stage-specific mouse embryonic antigen (SSEA-1). *Proc. natl. Acad. Sci. USA* 75, 5565-5569.
- Recent progress in identifying genes regulating hematopoietic stem cell function and fate Craig T Jordan, Gary Van Zant *Current Opinion in Cell Biology* 1998, 10:716-720.
- Singer MJ, Selker EU. Genetic and epigenetic inactivation of repetitive sequences in *Neurospora crassa*: RIP, DNA methylation, and quelling. *Curr Top Microbiol Immunol.* 1995;197:165-77.
- Matzke MA, Matzke AJ. Gene silencing in plants: relevance for genome evolution and the acquisition of genomic methylation patterns. *Novartis Found Symp.* 1998;214:168-80; discussion 181-6. Review.
- Stam M, de Bruin R, van Blokland R, van der Hoorn RA, Mol JN, Kooter JM. Distinct features of post-transcriptional gene silencing by antisense transgenes in single copy and inverted T-DNA repeat loci. *Plant J.* 2000 Jan;21(1):27-42.
- Montgomery MK, Xu S, Fire A. RNA as a target of double-stranded RNA-mediated genetic interference in *Caenorhabditis elegans*. *Proc Natl Acad Sci U S A.* 1998 Dec 22;95(26):15502-7.
- Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature.* 1998 Feb 19;391(6669):806-11.
- Kennerdell JR, Carthew RW. Heritable gene silencing in *Drosophila* using double-stranded RNA. *Nat Biotechnol.* 2000 Aug;18(8):896-898.

- Shi H, Djikeng A, Mark T, Wirtz E, Tschudi C, Ullu E. Genetic interference in *Trypanosoma brucei* by heritable and inducible double-stranded RNA. *RNA*. 2000 Jul;6(7):1069-76.
- 5 Wianny F, Zernicka-Goetz M. Specific interference with gene function by double-stranded RNA in early mouse development. *Nat Cell Biol*. 2000 Feb;2(2):70-5
- Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM. Embryonic stem cell lines derived from human blastocysts. *Science*. 1998 Nov 6;282(5391):1145-7.
- 10 Thomson JA, Kalishman J, Golos TG, Durning M, Harris CP, Becker RA, Hearn JP. Isolation of a primate embryonic stem cell line. *Proc Natl Acad Sci U S A*. 1995 Aug 15;92(17):7844-8.
- 15 Prober JM, Trainor GL, Dam RJ, Hobbs FW, Robertson CW, Zagursky RJ, Cocuzza AJ, Jensen MA, Baumeister K. A system for rapid DNA sequencing with fluorescent chain-terminating dideoxynucleotides. *Science*. 1987 Oct 16;238(4825):336-41.
- 20 Feinberg AP, Vogelstein B. A technique for radiolabeling DNA restriction endonuclease fragments to high specific activity. *Anal Biochem*. 1983 Jul 1;132(1):6-13.
- 25 Mullis KB, Faloona FA. Specific synthesis of DNA in vitro via a polymerase-catalyzed chain reaction. *Methods Enzymol*. 1987;155:335-50.
- Scholer HR, Hatzopoulos AK, Balling R, Suzuki N, Gruss P. A family of octamer-specific proteins present during mouse embryogenesis: evidence for germline-specific expression of an Oct factor. *EMBO J*. 1989 Sep;8(9):2543-50.
- 30

- Kraft HJ, Mosselman S, Smits HA, Hohenstein P, Piek E, Chen Q, Artzt K, van
Zoelen EJ. Oct-4 regulates alternative platelet-derived growth factor alpha receptor
gene promoter in human embryonal carcinoma cells. J Biol Chem. 1996 May
5 31;271(22):12873-8.
- Reubinoff BE, Pera MF, Fong CY, Trounson A, Bongso A. Embryonic stem cell
lines from human blastocysts: somatic differentiation in vitro. Nat Biotechnol. 2000
Apr;18(4):399-404.
- 10 Shamlott MJ, Axelman J, Wang S, Bugg EM, Littlefield JW, Donovan PJ,
Blumenthal PD, Huggins GR, Gearhart JD. Derivation of pluripotent stem cells from
cultured human primordial germ cells. Proc Natl Acad Sci U S A. 1998 Nov
10;95(23):13726-31.
- 15 Clarke DL, Johansson CB, Wilbertz J, Veress B, Nilsson E, Karlstrom H, Lendahl U,
Frisen J. Generalized potential of adult neural stem cells. Science. 2000 Jun
2;288(5471):1660-3.

20

25

30

CLAIMS

1. A method to modulate the differentiation state of a stem cell comprising:
 - i) contacting a stem cell with at least one nucleic acid molecule comprising a
5 sequence of a gene which mediates at least one step in the differentiation of said cell
which nucleic acid molecule consists of a first part linked to a second part wherein
said first and second parts are complementary over at least part of their length and
further wherein said first and second parts form a double stranded region by
complementary base pairing over at least part of their length;
 - 10 (ii) providing conditions conducive to the growth and differentiation of the cell
treated in (i) above; and optionally
 - (iii) maintaining and/or storing the cell in a differentiated state.
2. A method according to Claim 1 wherein said first and second parts are linked
15 by at least one nucleotide base.
3. A method according to Claim 1 or 2 wherein said nucleic acid molecule is a
stem loop RNA molecule or a nucleic acid molecule or a vector encoding said stem
loop RNA.
20
4. A method according to any of Claims 1-3 wherein said conditions are *in vitro*
cell culture conditions.
5. A method according to any of Claims 1-4 wherein said stem cell is selected
25 from the group consisting of: an embryonic stem cell; an embryonic germ cell; an
embryonal carcinoma cell; a haemopoietic stem cell; a muscle stem cell; a nerve
stem cell; a skin dermal sheath stem cell; a liver stem cell; a teratocarcinoma cell.
6. A method according to any of Claims 1-5 wherein said stem cell is an
30 embryonic stem cell or embryonic germ cell.

7. A method according to any of Claims 1-6 wherein said nucleic acid molecule is derived from at least one nucleic acid sequence as represented by Figures 4- 54.
8. A RNA molecule derived from a coding sequence of at least one gene involved in stem cell differentiation comprising a first part linked to a second part wherein said first and second parts are complementary over at least part of their length and further wherein said first and second parts form a double stranded region by complementary base pairing over at least part of their length.
9. A RNA molecule according to Claim 8 wherein said first and second parts are linked by at least one nucleotide base (nb).
10. A RNA molecule according to Claim 9 wherein said first and second parts are linked by 2, 3, 4, 5, 6, 7, 8, 9, or 10nb in length.
11. A RNA molecule according to Claim 9 wherein said linker is at least 10nb in length.
12. A RNA molecule according to any of Claims 8-11 wherein the length of the RNA molecule is between 10nb –1000nb in length.
13. A RNA molecule according to Claim 12 wherein the length of the RNA molecule is selected from 10nb; 20nb; 30nb; 40nb; 50nb; 60nb; 70nb; 80nb; 90nb in length.
14. A RNA molecule according to Claim 12 wherein said RNA molecule is 100nb; 200nb; 300nb; 400nb; 500nb; 600nb; 700nb; 800nb; 900nb; or 1000nb in length.
15. A RNA molecule according to Claim 8 wherein said RNA molecule is at least 1000nb in length.

16. A RNA molecule according to Claim 8 wherein said RNA molecule is 21nb in length.

5 17. A RNA molecule according to any of Claims 8 -16 wherein said RNA molecule comprises sequences identified in Figures 4-54.

18. A RNA molecule according to any of Claims 8-17 wherein said RNA molecules comprise modified nucleotide bases.

10

19. A nucleic acid molecule which encodes an RNA molecule according to any of Claims 8-18 wherein said nucleic acid molecule is operably linked to at least one further nucleic acid molecule capable of promoting transcription of said nucleic acid linked thereto.

15

20. A nucleic acid molecule according to Claim 19 wherein said further nucleic acid molecule is a promoter capable of inducible transcription.

21. A vector including a nucleic acid molecule according to Claim 19 or 20.

20

22. A cell transfected with an RNA molecule according to any of Claims 8-18, nucleic acid molecule according to Claim 19 or 20 or a vector according to Claim 21.

25 23. A cell according to Claim 22 wherein said cell is an embryonic stem cell or embryonic germ cell.

24. A cell according to Claim 22 wherein said cell is an embryonal carcinoma cell.

30

25. A method to manufacture stem loop RNA molecules comprising:

- (i) providing a nucleic acid molecule according to Claim 19 or 20 or a vector according to Claim 21;
- 5 (ii) providing reagents and conditions which allow the synthesis of the RNA molecule comprising a RNA molecule according to any of Claims 8-18; and
- (iii) providing conditions which allow the RNA molecule to base pair over at least part of its length, or at least that part corresponding to the nucleic acid sequence
- 10 encoding said stem cell gene which mediates stem cell differentiation.
26. An *in vivo* method to promote the differentiation of stem cells comprising administering to an animal an effective amount of an RNA molecule according to any of Claims 8-18, a nucleic acid molecule according to Claim 19 or 20 or a vector
- 15 according to Claim 21, sufficient to effect differentiation of a target stem cell.
27. A RNA molecule according to any of Claims 8-18, a nucleic acid molecule according to Claim 19 or 20 or a vector according to Claim 21 for use as a pharmaceutical.
- 20
28. A pharmaceutical composition comprising a RNA molecule according to any of Claims 8-18, a nucleic acid molecule according to Claim 19 or 20 or a vector according to Claim 21.
- 25
29. Use of a RNA molecule according to any of Claims 8-18, a nucleic acid molecule according to Claim 19 or 20 or a vector according to Claim 21 for the manufacture of a medicament for use in promoting the differentiation of stem cells to provide differentiated cells/tissues to treat diseases where cell/tissues are destroyed by said disease.
- 30

30 Use according to Claim 29 wherein said disease is selected from the group
consisting of: pernicious anemia; stroke, neurodegenerative diseases such as
Parkinson's disease, Alzheimer's disease; coronary heart disease; cirrhosis;
diabetes; nerves damaged as a consequence of trauma (e.g. replacement of spinal
5 cord tissue).

31. A cell obtainable by the method according to any of Claims 1-7.

32. An organ comprising at least one cell according to Claim 31.
10

33. A non-human transgenic animal comprising a RNA molecule according to
any of Claims 8-18, or a nucleic acid molecule according to Claim 19 or 20, or a
vector according to Claim 21.

15

20

25

30

Figure 1

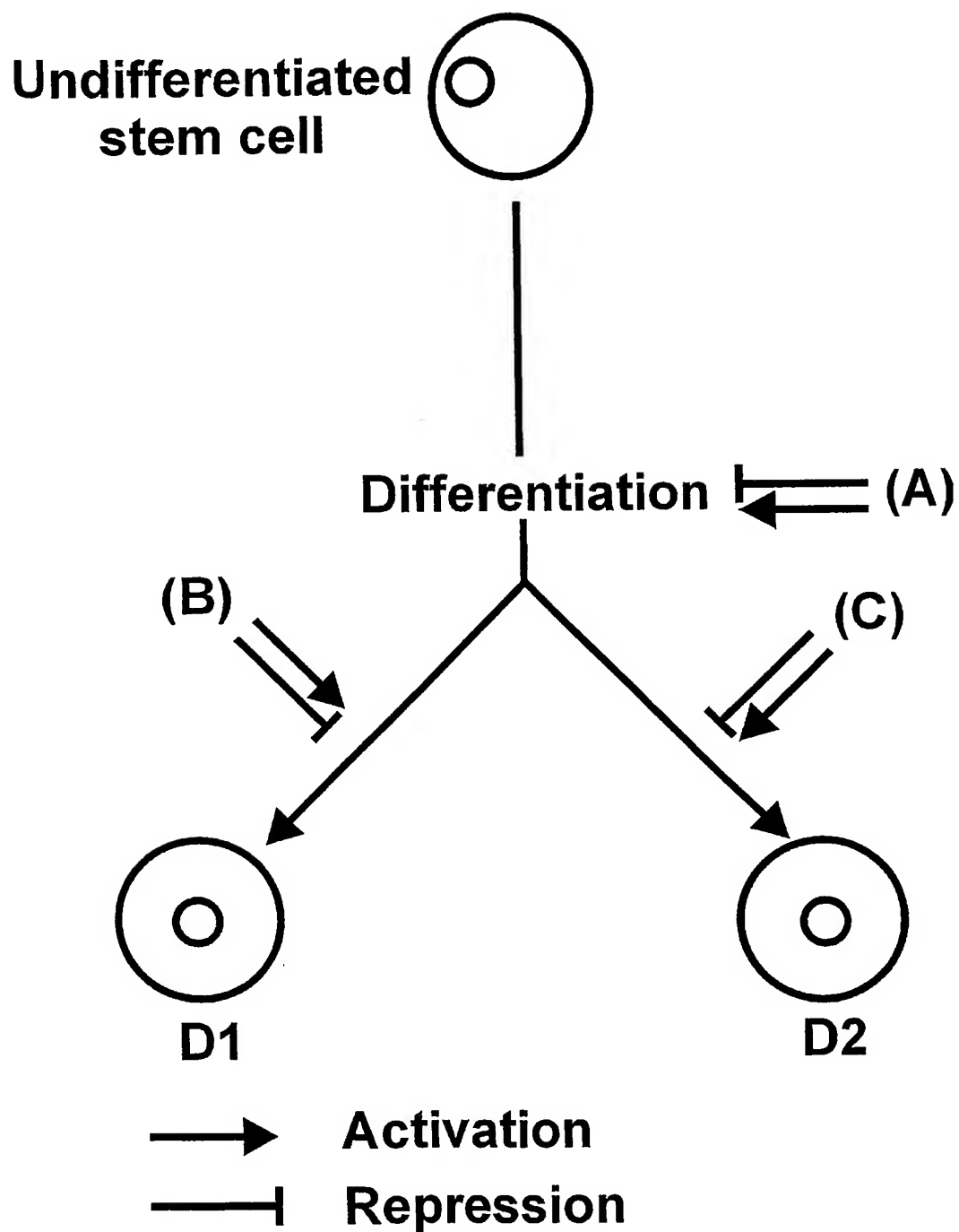


Figure 2

5'
AGCAGCTTGGGCTCGAGAAGGATGTGGTCCGAGTGTGGTTCTGTAACCGGCGCCAG
AAGGGCAAGCGATCAAGCAGCGACTATGCACAACGAGAGGATTTTGAGGCTGCTGG
GTCTCCTTTCTCAGGGGGACCAGTGTCTTTTCCTCTGGCCCCAGGGCCCCATTTTGGT
GCCCCAGGCTATGGGAGCCCTCACTTCACTGCACTGTACTCCTCGGTCCCTTTCCCTG
AGGGGGAAGCCTTTCCCCCTGTCTCTGTCACCACTCTGGGCTCTCCCTTGCATTCAA
CTGAGGTGCCTGCCTGCCCTTCTAGGAATGGGGGACAGGGGGAGGGGAGGAGCTAG
GGAAAGAAAACCTGGAGTTTGTGCCAGGGTTTTTGGATTAAGTTCTTCATTCACTAA
GGAAGGAATTGGGAACACAAAGG
3'

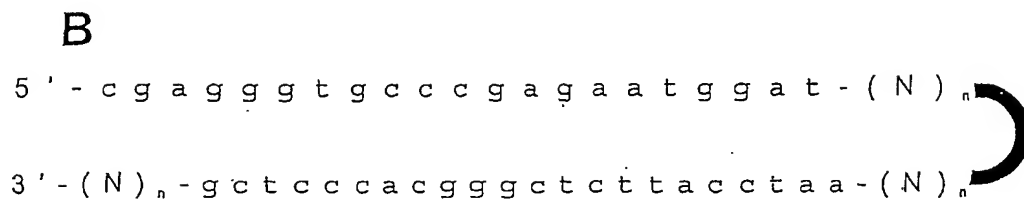
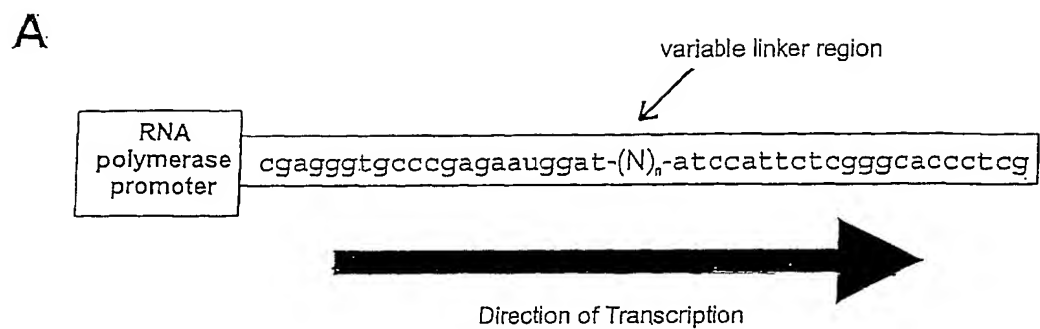


Figure 3

CTGCTCGCCCTGCTCTGTGCCCTGCGAGCCAAGGTGTGCGGGGCCTCGGGTCAGTTTGAGCTGG
AGATCCTGTCCATGCAGAACGTGAATGGAGAGCTACAGAATGGGAACTGTTGTGGTGGAGTCC
GGAACCCTGGCGACCGCAAGTGCACCCGCGACGAGTGTGATACGTAACCTTCAAAGTGTGCCTCA
AGGAGTATCAGTCCCGCGTCACTGCCGGGGGACCCTGCAGCTTCGGCTCAGGGTCTACGCCTGT
CATCGGGGGTAACACCTTCAATCTCAAGGCCAGCCGTGGCAACGACCGTAATCGCATCGTACTG
CCTTTCAGTTTCGCCTGGCCGAGGTCTACACTTTGCTGGTGGAGGCCTGGGATTCCAGTAATG
ACACTATTCAACCTGATAGCATAATTGAAAAGGCTTCTCACTCAGGCATGATAAACCTAGCCG
GCAATGGCAGACACTGAAACAAAACACAGGGATTGCCACTTCGAGTATCAGATCCGAGTGAC
CTGTGATGACCACTACTATGGCTTTGGCTGCAATAAGTTCTGTCTGCCAGAGATGACTTCTTTG
GACATTATGCCTGTGACCAGAACGGCAACAAACTTGCATGGAAGGCTGGATGGGTCTCTGATT
GCAACAAAGCTATCTGCCGACAGGGCTGCAGTCCCAAGCATGGGTCTTGTAACCTTCCAGGTG
ACTGCAGGTGCCAGTACGGTTGGCAGGGCCTGTACTGCGACAAGTGCATCCCGCACCCAGGAT
GTGTCCACGGCACCTGCAATGAACCCTGGCAGTGCCTCTGTGAGACCAACTGGGGTGGACAGC
TCTGTGACAAAGATCTGAATTACTGTGGGACTCATCAGCCCTGTCTCAACCGGGGAACATGTAG
CAACACTGGGCCTGACAAATACCAGTGCTCCTGCCAGAGGGCTACTCGGGCCCCAACTGTGA
AATTGCTGAGCATGCTTGTCTCTGTGACCCCTGCCATAACCGAGGCAGCTGCAAGGAGACCTCC
TCAGGCTTTGAGTGTGAGTGTCTCCAGGCTGGACTGGCCCCACGTGTTCCACAAACATCGATG
ACTGTTCTCCAAATAACTGTTCCCATGGGGGCACCTGCCAGGATCTGGTGAATGGATTCAAGTG
TGTGTGCCCGCCCCAGTGGACTGGCAAGACTTGTGAGTTAGATGCAAAATGAGTGCAGGGCCAA
ACCTTGTGTAAATGCCAGATCCTGTAAGAATCTGATTGCCAGCTACTACTGTGATTGCCTTCTG
GCTGGATGGGTGAGAACTGTGACATAAATATCAATGACTGCCTTGGCCAGTGTGAGAATGACG
CCTCCTGTGCGGATTGGTTAATGGTTATCGCTGTATCTGTCCACCTGGCTATGCAGGCGATCAC
TGTGAGAGAGACATCGATGAGTGTGCTAGCAACCCCTGCTTGAATGGGGGTCACTGTGAGAAT
GAAATCAACAGATTCCAGTGTCTCTGTCCCACTGGTTTCTCTGGAAACCTCTGTGAGCTGGACA
TCGATTACTGCGAGCCCAACCCCTTGCCAGAATGGCGCCCAGTGTACAATCGTGCCAGTGACTA
TTTCTGCAAGTGCCCCGAGGACTATGAGGGCAAGAACTGCTCACACCTGAAAGACCACTGCCG
TACCACCACCTGCGAAGTGATTGACAGCTGCACTGTGGCCATGGCCTCCAACGACACGCCTGAA
GGGGTGGGTATATCTCTTCTAACGTCTGTGGTCCCCATGGGAAGTGCAAGAGCCAGTCGGGAG
GCAAAATCACCTGTGACTGTAACAAAGGCTTACCGGCACCTACTGCCATCGATGGCGTTAACTCCTACAAGTGT
ATCTGTAGTGACGGCTGGGAGGGAGCGCACTGTGAGAACATAAATGACTGTAGCCAGAAC
CCTTGTACTACGGGGGTACATGTGCGAGACCTGGTCAATGACTTTTACTGTGACTGCAAAAATG
GCTGGAAAGGAAAGACTTGCCATTCCCGTGACAGCCAGTGTGACGAAGCCACGTGTAATAATG
GTGGTACCTGCTATGATGAAGTGGACACGTTTAAAGTGCATGTGTCCCGGTGGCTGGGAAGGAA
CAACTTGTAATATAGCTAGAAACAGTAGCTGCCTGCCGAACCCCTGTCATAATGGAGGTACCTG
CGTGGTCAATGGAGACTCCTTACCTGTGTCTGCAAAGAAGGCTGGGAGGGGCCTATTTGTA
CAAAATACCAACGACTGCAGTCCCCATCCTTGTACATAAGCGGGACCTGTGTGGACGGAGAC
AACTGGTATCGGTGCGAATGTGCCCCGGGTTTTGCTGGGCCAGACTGCAGGATAAACATCAATG
AGTGCCAGTCTTCCCTTGTGCCTTTGGGGCCACCTGTGTGGATGAGATCAATGGCTACCAGTG
TATCTGCCCTCCAGGACATAGTGGTGCCAAGTGCCATGAAGTTTCAGGGCGATCTTGATCACC
ATGGGGAGAGTGATACTTGATGGGGCCAAGTGGGATGATGACTGTAACACCTGCCAGTGCCTG
AATGGACGGGTGGCCTGCTCCAAGGTCTGGTGTGGCCGAGACCTTGCAGGCTCCACAAAAGC
CACAATGAGTGCCCCAGTGGGCAGAGCTGCATCCCGGTCTGGATGACCAGTGTTTCGTGCGCC
CCTGCACTGGTGTGGCGAATGTGGTCTCCAGCCTCCAGCCAGTGAAGACCAAGTGCACATC
TGACTCCTATTACCAGGATAACTGTGCAACATCACTTTACCTTTAACAAGAGATGATGTCT
CCAGGTCTTACCACCGAACACATTTGCAGCGAATTGAGGAATTTGAATATCCTGAAGAATGTTT
CTGCTGAATATTCGATCTACATAGCCTGTGAGCCTTCCCTGTGAGCAACAAATGAAATACACGT
GGCCATCTCTGAGAAAGACATCCGGGATGATGGGAACCCCTGTCAAGGAAATTACCGATAAAAT
AATAGATCTCGTTAGTAAACGGGATGGAAACAGCTCACTTATTGCTGCGGTTGCAGAAAGTCAG
AGTTCAGAGGCGTCTCTGAAAAACAGAACAGATTTCTGGTTCTCTGTGAGCTCTGTCTTA
ACAGTGGCTTGGGTCTGTTGCTTGGTGACAGCCTTCTACTGGTGTGTACGGAAGCGGCGGAAGC
CCAGCAGCCACACTCACTCCGCCCCGAGGACAACACCAACCAACATGTGCGGGGAGCTGA
ACCAAAATCAAAAACCCCATCGAGAAACACGAGACCAACACGGTCCCCATTAAGGATTACGAGA
ACAAAAACTCCAAAATGTCAAAAATCAGGACACAACTCGGAAGTGGAGGAGGATGACATG
GATAAACACAGCAGAAAGTCCGCTTTGCCAAACAGCCAGTGTATACGCTGGTAGACAGAGAG
GAGAAGGCCCCCAGCGGCACGCGGACAAAAACCCGAACTGGACAAATAAACAGGACAACAG

AGACTTGGAAGTGTCCAGAGCTTGAACCGGATGGAATACATCGTATAGCAGACAGTGGGCTG
CCGCCATAGGTAGAGTTTGAGGGCACCGCGGGCCG

Figure 5

CTGCGGCCGGCCGCGAGCTAGGCTGGGTTTTTTTTTCTCCCCTCCCTCCCCCTTTTTCCATGCAGC
TGATCTAAAAGGGAATAAAAGGCTGCGCATAATCATAATAATAAAGAGGGGAGCGCGAGAGAAGGA
GAAAGCCGGGAGGTGGAAGAGGAGGGGGAGCGTCTCAAAGAAGCGATCAGAATAATAAAGGAGGCGG
CTCTTTGCCCTTCTGGAACGGGCCGCTCTTGAAAGGGCTTTTGAAAAGTGGTGTTGTTTCCAGTCGTGCA
TGCTCCAATCGGCGGAGTATATTAGAGCCGGGACGCGCGGCCGAGGGGCAGCGGCGACGGCAGCACG
GCGGCAGCACCGCGCAACAGCAGCGGCGGCGTCCCGAGTGGCCGCGGCGCGGGCGCAGCGATGCGT
CCCCACGGACGCGCGGCCGTCGCGGCGCCCCCTAAGCCTCCTGCTCGCCCTGCTCTGTGCCCTGCGAGC
CAAGGTGTGTGGGGCCTCGGGTCACTTCGAGTTGGAGATCCTGTCCATGCAGAACGTGAACGGGGAGCTG
CAGAACGGGAAGTGTGCGGCGGCGCCCGGAACCCGGGAGACCGCAAGTGCACCCGCGACGAGTGTGAA
CATACTTCAAAGTGTGCCTCAAGGAGTATCAGTCCCGCGTCACGGCCGGGGGGCCCTGCAGCTTCGGCTC
AGGGTCCACGCTGTCTCGGGGGCAACACCTTCAACCTCAAGGCCAGCCGCGCAACGACCGCAACCC
ATCGTGCTGCCTTTCAGTTTCGCCTGGCCGAGGTCCTATACGTTGCTTGTGGAGGCGTGGGATTCCAGTA
ATGACACCGTTCAACCTGACAGTATTATTGAAAAGGCTTCTCACTCGGGCATGATCAACCCAGCCGGCA
GTGGCAGACGCTGAAGCAGAACACGGGCGTTGCCACTTTGAGTATCAGATCCGCGTGACCTGTGATGAC
TACTACTATGGCTTTGGCTGCAATAAGTTCTGCCGCCCCAGAGATGACTTCTTTGGACACTATGCCCTGTG
ACCAGAATGGCAACAAACTTGCATGGAAGGCTGGATGGGCCCCGAATGTAACAGAGCTATTTGCCGAA
AGGCTGCAGTCTAAGCATGGGTCTTGCAAACCTCCAGGTGACTGCAGGTGCCAGTATGGCTGGCAAGGC
CTGTACTGTGATAAGTGCATCCACACCCGGGATGCGTCCACGGCATCTGTAATGAGCCCTGGCAGTGCC
TCTGTGAGACCAACTGGGGCGGCCAGCTCTGTGACAAAGATCTCAATTACTGTGGGACTCATCAGCCGTG
TCTCAACGGGGGAACCTGTAGCAACACAGGCCCTGACAAATATCAGTGTTCCTGCCCTGAGGGGTATTCA
GGACCAACTGTGAAATTGCTGAGCACGCCTGCCTCTCTGATCCCTGTCACAACAGAGGCAGCTGTAAGG
AGACCTCCCTGGGCTTTGAGTGTGAGTGTTCGCCAGGCTGGACCGGCCCCACATGCTCTACAAACATTGA
TGACTGTTCTCTAATAACTGTTCCACGGGGGCACCTGCCAGGACCTGGTTAACGGATTTAAGTGTGTG
TGCCCCCAGAGTGGACTGGGAAAACGTGCCAGTTAGATGCAAATGAATGTGAGGGCAAACCTTGTGTAA
ACGCCAAATCCTGTAAGAATCTCATTGCCAGTACTACTGCGACTGTCTTCCCGGCTGGATGGGTGAGAA
TTGTGACATAAATATTAATGACTGCCTTGGCCAGTGTGAGAATGACGCCTCCTGTGCGGATTTGGTTAAT
GGTTAATCGCTGTATCTGTCCACCTGGCTATGCAGGCGATCACTGTGAGAGAGACATCGATGAATGTGCCA
GCAACCCCTGTTTGAATGGGGGTCACTGTGAGAATGAAATCAACAGATTCCAGTGTCTGTGTCCCACTGG
TTTCTCTGGAAACCTCTGTGAGCTGGACATCGATTATTGTGAGCCTAATCCCTGCCAGAACGGTGCCAG
TGCTACAACCGTGCCAGTGACTATTTCTGCAAGTGCCCGAGGACTATGAGGGCAAGAACTGCTCACACC
TGAAAGACCACTGCCGACGACCCCTGTGAAGTGATTGACAGCTGCACAGTGGCCATGGCTTCCAACGA
CACACCTGAAGGGGTGCGGTATATTTCTCCAACGTCTGTGGTCCTCACGGGAAGTGCAAGAGTCAGTCG
GGAGGCAAAATCACCTGTGACTGTAACAAAGGCTTCACGGGAACATACTGCCATGAAAATTAATGACT
GTGAGAGCAATTCCTGTAGAAACGGTGGCAGTGTGATCGATGGTGTCAACTCCTACAAAGTGCATCTGTAG
TGACGGCTGGGAGGGGGCCTACTGTGAAACCAATATTAATGACTGCAGCCAGAACCCCTGCCACAATGG
GGCAGTGTGCGACCTGGTCAATGACTTCTACTGTGACTGTAAAAATGGGTGGAAAGGAAAGACCTGCC
ACTCACGTGACAGTCAGTGTGATGAGGCCACGTGCAACAACGGTGGCACCTGCTATGATGAGGGGGATC
TTTTAAGTGCATGTGTCTGGCGGCTGGGAAGGAACAACCTGTAACATAGCCCCGAAACAGTAGCTGCCTG
CCCAACCCCTGCCATAATGGGGGCACATGTGTGGTCAACGGCGAGTCCTTTACGTGCGTCTGCAAGGAAG
GCTGGGAGGGGCCCATCTGTGCTCAGAATACCAATGACTGCAGCCCTCATCCCTGTTACAACAGCGGCAC
CTGTGTGGATGGAGACAACTGGTACCGGTGCGAATGTGCCCGGGTTTTGCTGGGCGGACTGCAGAATA
AACATCAATGAATGCCAGTCTTCACTTGTGCGTTTGGAGCGACCTGTGTGGATGAGATCAATGGCTACC
GGTGTGTCTGCCCTCCAGGGCACAGTGGTGCCAAGTGCCAGGAAGTTTCAGGGAGACCTTGCATCACCAT
GGGGAGTGTGATAACAGATGGGGCCAAATGGGATGATGACTGTAATACCTGCCAGTGCCTGAATGGACG
ATCGCTGCTCAAAGGTCTGGTGTGGCCCTCGACCTTGCCTGCTCCACAAAGGGGCACAGCGAGTGCCCCA
GCGGGCAGAGCTGCATCCCCATCCTGGACGACCAAGTGCTTCCGTCCACCCCTGCACTGGTGTGGGCGAGTG
TCGGTCTTCCAGTCTCCAGCCGGTGAAGACAAAGTGCACCTCTGACTCCTATTACCAGGATAACTGTGCG
AACATCAATTTACCTTTAACAAGGAGATGATGTACCAAGGTCTTACTACGGAGCATTTCGACTGAAT
TGAGGAATTTGAATATTTTGAAGAATGTTTCCGCTGAATATTCAATCTACATCGCTTGCAGGCTTCCCC
TTCAGCGAATGAATGAAATACATGTGGCCATTTCTGCTGAAGATATACGGGATGATGGGAACCCGATCAAG
GAAATCACTGACAAAATAATCGATCTTGTTAGTAAACGTGATGGAAAACAGCTCGCTGATTGCTGCCGTTG
CAGAAGTAAGAGTTCAGAGGCGGCTCTGAAGAACAGAACAGATTTCCTTGTTCCTTGTGAGCTCTGT
CTTAAGTGTGGCTTGGATCTGTTGCTTGGTGACGGCCTTCTACTGGTGCCTGCGGAAGCGGCGGAAGCCG
GGCAGCCACACACTCAGCCTCTGAGGACAACACCACCAACAACGTGCGGGAGCAGCTGAACCAGATA

AAAACCCCATTGAGAAACATGGGGCCAACACGGTCCCCATCAAGGATTACGAGAACAAGAACTCCAAAT
GTCTAAAATAAGGACACACAATTCTGAAGTAGAAGAGGACGACATGGACAAACACCAGCAGAAAGCCCCG
GTTTGCCAAGCAGCCGCGTATACGCTGGTAGACAGAGAAGAGAAGCCCCCAACGGCAGCCGACAAC
ACCCAAACTGGACAAACAAACAGGACAAACAGAGACTTGGAAAGTGCCAGAGCTTAAACCGAATGGAGA
CATCGTATAGCAGACCGCGGGCACTGCCGCCGCTAGGTAGAGTCTGAGGGCTTGTAGTTCTTTAAACTGT
CGTGTCTACTCGAGTCTGAGGCCGTTGCTGACTTAGAATCCCTGTGTTAATTTAAGTTTTGACAAGCTG
GCTTACACTGGCAATGGTAGTTTCTGTGGTTGGCTGGGAAATCGAGTGCCGCATCTCACAGCTATGCAAA
AAGCTAGTCAACAGTACCCTGGTTGTGTGCCCTTGCAGCCGACACGGTCTCGGATCAGGCTCCCAGGA
GCCTGCCAGCCCCCTGGTCTTTGAGCTCCCACTTCTGCCAGATGTCCTAATGGTGATGCAGTCTTAGAT
CATAGTTTTATTTATATTTATTGACTCTTGAGTTGTTTTGTATATTGGTTTTATGATGACGTACAAGTA
GTTCTGTATTTGAAAGTGCCTTTGCAGCTCAGAACCACAGCAACGATCACAAATGACTTTATTATTTATT
TTTTTAATTGTATTTTGTGTGGGGGAGGGGAGACTTTGATGTCAGCAGTTGCTGGTAAATGAAGAA
TTTAAAGAAAAAATGTCAAAAGTAGAACTTTGTATAGTTATGTAAATAATCTTTTTTATTAATCACTG
TGTATATTTGATTTATTAACCTTAATAATCAAGAGCCTTAAACATCATTCCCTTTTTATTTATATGTATGT
GTTTAGAATTGAAGGTTTTTGATAGCATTGTAAGCGTATGGCTTTATTTTTTTGAACTCTTCTCATTACT
TGTGCCCTATAAGCCAAAATTAAGGTGTTTGAAAATAGTTTATTTTAAACAATAGGATGGGCTTCTGTG
CCCAGAATACTGATGGAATTTTTTTTGTACGACGTCAGATGTTTAAACACCTTCTATAGCATCACTTAA
AACACGTTTTAAGGACTGACTGAGGCAGTTGAGGATTAGTTTGAACAGGTTTTTTTGTGTGTGTGT
TTTGTTTTTCTGCTTTAGACTTGAAAAGAGACAGGCAGGTGATCTGCTGCAGAGCAGTAAGGGAACAAGT
TGAGCTATGACTTAACATAGCCAAAATGTGAGTGTTGAATATGATTAAAAATATCAAATTAATTGTGTG
AACTTGGAAGCACACCAATCTGACTTTGTAAATCTGATTTCTTTTACCATTCTGTACATACTGAAC
CACTTGATAGATTTGATTTTTTTTTTAATCTACTGCATTTAGGGAGTATTCTAATAAGCTAGTGAATACT
TGAACCATAAAATGTCCAGTAAGATCACTGTTTAGATTGGCCATAGAGTACACTGCCTGCCTTAAGTGAG
GAAATCAAAGTGCTATTACGAAGTTCAAGATCAAAAAGGCTTATAAAACAGAGTAATCTTGTGTGTTTCAG
CATTGAGACCGTGAAGATACTTTGTATTGTCCTATTAGTGTATATGAACATACAAATGCATCTTTGATG
TGTTGTTCTTGGAATAAAATTTGAAAAGTAATATTTATTAATTTTTTTGTATGAAAACATGGAACAGT
GTGGCTCTTCTGAGCTTACGTAGTTCTACCGGCTTTGCCGTGTGCTTCTGCCACCCTGCTGAGTCTGTT
TGGTAATCGGGGTATAATAGGCTCTGCCTGACAGAGGGATGGAGGAAGAACTGAAAGGCTTTTCAACCC
AAAACTCATCTGGAGTTCTCAAAGACCTGGGGCTGCTGTGAAGCTGGAAGCTGCGGGAGCCCCATCTAGGG
GAGCCTTGATTCCCTTGTATTCAACAGCAAGTGTGAATACTGCTTGAATAAACACCACTGGATTAATGG
AAAAAAAAAAAAAAAA

Figure 6

GGAGCGGGCGCGCGCGCGGGCGCGGGGCCGCGCGGGCGGGTTCGCGGGGGCAATGCGGGCGCAGGGCCG
GGGCCTTCCCCCGCGCTGCTGCTGCTGCTGGCGCTCTGGGTGCAGGCGGCGCGGCCCATGGGCTATTT
CGAGCTGCAGCTGAGCGCGCTGCGGAACGTGAACGGGGAGCTGCTGAGCGGCGCCTGCTGTGACGGCGC
GGCCGGAACAACGCGCGCGGGGGGCTGCGGCCACGACGAGTGCGACACGTACGTGCGCGTGTGCCTTAAG
AGTACCAGGCCAAGGTGACGCCCCACGGGGCCCTGCAGCTACGGCCACGGCGCCACGCCCCGTGTGGCG
CAACTCCTTCTACCTGCCGCGCGGGCGCTGCGGGGACCGAGCGCGCGCGCGGCCCGGGCGCGC
GACCAGGACCCGGGCTTCGTGCTCATCCCTTCCAGTTTCGCTGCGCGCGCTCCTTTACCTCATCGTGG
AGGCCTGGGACTGGGACAACGATACCAACCCGAATGAGGAGCTGCTGATCGAGCGAGTGTGCGATGCCG
CATGATCAACCCGAGGACCGCTGGAAGAGCCTGCACTTCAGCGGCCACGTGGCGCACCTGGAGCTGCG
ATCCGCGTGCCTGCGACGAGAACTACTACAGCGCCACTTGCAACAAGTTCTGCCGCCCCGCAACGACT
TTTTCGGCCACTACACCTGCGACCACTACGGCAACAAGGCCTGCATGGACGGCTGGATGGGCAAGGAGTG
CAAGGAAGCTGTGTGTAACAAGGGTGTAATTTGCTCCACGGGGGATGCACCGTGCCTGGGGAGTGCA
TGCAGCTACGGCTGGCAAGGGAGGTTCTGCGATGAGTGTGTCCCTACCCCGGCTGCGTGCATGGCAGTT
GTGTGGAGCCCTGGCAGTGCAACTGTGAGACCACTGGGGCGGCTGCTCTGTGACAAAGACCTGAACCTA
CTGTGGCAGCCACCAACCCCTGCACCAACGAGGACGTGCATCAACGCCGAGCCTGACCAGTACCGCTGC
ACCTGCCCTGAGCCTACTCGGGCAGGAAGTGTGAGAAGGCTGAGCACGCCTGCACCTCCAACCCGTGTG
CCAACGGGGGCTCTTGCCATGAGGTGCCGTCCGGCTTCGAATGCCACTGCCCATCGGGCTGGAGCGGGCC
CACCTGTGCCCTTGACATCGATGAGTGTGCTTCGAACCCGTGTGCGGCCGCTGGCACCTGTGTGGACCAG
GTGGACGGCTTTGAGTGCATCTGCCCCGAGCAGTGGGTGGGGGCCACCTGCCAGCTGGACGTCAACGACT
GTGAAGGGAAGCCATGCCTTAACGCTTTTTCTGCAAAAACCTGATTGGCGGCTATTACTGTGATTGCAT
CCCGGGCTGGAAGGGCATCAACTGCCATATCAACGTCAACGACTGTGCGGGCAGTGTGAGCATGGGGC
ACCTGCAAGGACCTGGTGAACGGGTACCAAGTGTGTGTGCCACGGGGCTTCGGAGGCGCGGCTTCGGAGC
TGAACGAGACAAGTGTGCCAGCAGCCCTGCCACAGCGCGGCTCTGCGAGGACCTGGCCGACGGCT
CCACTGCCACTGCCCCAGGGCTTCTCCGGGCTCTCTGTGAGGTGGATGTGACCTTTGTGAGCCAAGC
CCCTGCCGGAACGGCGCTCGCTGCTATAACCTGGAGGGTGAATTAATGCGCCTGCCCTGATGACTTTG
GTGGCAAGAACTGCTCCGTGCCCGCGAGCCGTGCCCTGGCGGGGCTGCAGAGTATCGATGGCTGCGG

GTCAGACGCGGGGCTGGGATGCCTGGCACAGCAGCCTCCGGCGTGTGTGGCCCCCATGGACGCTGCGTC
AGCCAGCCAGGGGGCAACTTTTCCTGCATCTGTGACAGTGGCTTTACTGGCACCTACTGCCATGAGAACA
TTGACGACTGCCTGGGCCAGCCCTGCCGCAATGGGGGCACATGCATCGATGAGGTGGACGCCTTCCGCTG
CTTCTGCCCCAGCGGCTGGGAGGGCGAGCTCTGCGACACCAATCCCAACGACTGCCTTCCCGATCCCTGC
CACAGCCGCGGCCGCTGCTACGACCTGGTCAATGACTTCTACTGTGCGTGCGACGACGGCTGGAAGGGCA
AGACCTGCCACTCACGCGAGTTCCAGTGCGATGCCTACACCTGCAGCAACGGTGGCACCTGCTACGACAG
CGGCGACACCTTCCGCTGCGCCTGCCCCCGGCTGGAAGGGCAGCACCTGCGCCGTCGCCAAGAACAGC
AGCTGCCTGCCAAACCCCTGTGTGAATGGTGGCACCTGCGTGGGCAGCGGGGCTCCTTCTCTGCATCT
GCCGGGACGGCTGGGAGGGTCTGTAATTGCACTACAATAACCAACGACTGCAACCCCTCTGCCCTTGCTACAA
TGGTGGCATCTGTGTTGACGGCGTCAACTGGTTCGCTGCGAGTGTGCACCTGGCTTCGCGGGGCTGAC
TGCCGCATCAACATCGACGAGTGCCAGTCTCGCCCTGTGCCTACGGGGCCACGTGTGTGGATGAGATCA
ACGGGTATCGCTGTAGCTGCCACCCGGCCGAGCCGGCCCCCGGTGCCAGGAAGTGATCGGGTTCGGGAG
ATCCTGCTGGTCCCGGGGCACTCCGTTCACACCGAAAGCTCCTGGGTGGAAGACTGCAACAGCTGCCGC
TGCCTGGATGGCCGCGCTGACTGCAGCAAGGTGTGGTGGGATGGAAGCCTTGTCTGCTGGCCGGCCAGC
CCGAGGCCCTGAGCGCCAGTGCCCACTGGGGCAAAGGTGCCTGGAGAAGGCCCCAGGCCAGTGTCTGG
ACCACCTGTGAGCCCTGGGGGGAGTGCGGCGCAGAAGAGCCACCGAGCACCCCTGCCTGCCACGCTC
GGCCACCTGGACAATAACTGTGCGCCGCTCACCTTGCATTTCACCCGTGACCAGTGCCCCAGGGCACCA
CGGTGGGCGCCATTTGCTCCGGGATCCGCTCCCTGCCAGCCACAAGGGCTGTGGCACGGGACCGCCTGCT
GGTGTGCTTTGCGACCGGGCGTCTCGGGGGCCAGTGCCGTGGAGGTGGCCGTGTCTTCAGCCCTGCC
AGGGACCTGCCTGACAGCAGCCTGATCCAGGGCGCGGCCACGCCATCGTGGCCGCCATCACCCAGCGG
GGAACAGCTCACTGCTCCTGGCTGTACCGAGGTCAAGGTGGAGACGGTTGTTACGGGCGGCTCTTCCAC
AGGTCTGCTGGTGCCTGTGCTGTGTGGTGCCTTCAGCGTGTGTGGCTGGCGTGCCTGCTGTGCGTG
TGGTGGACACGCAAGCGCAGGAAAGAGCGGGAGAGGAGCCGCTGCCGCGGGAGGAGAGCGCCAAAC
AGTGGGCCCCGCTCAACCCCATCCGCAACCCCATCGAGCGGCCGCGGGGGGCCACAAGGACGTGCTCTACCA
GTGCAAGAACTTCACGCGCGCCGCGCAGGGCGGACGAGGCGCTGCCCGGGCGGCCGCCACGCGGC
GTCAGGGAGGATGAGGAGGACGAGGATCTGGGCCGCGGTGAGGAGGACTCCCTGGAGGCGGAGAAAGTTC
TCTCACACAAATTCACCAAAGATCCTGGCCGCTCGCCGGGGAGGCCGCGCCACTGGGCCTCAGGCCCCAA
AGTGGACAACCGCGCGGTGAGGAGCATCAATGAGGCCGCTACGCCGGCAAGGAGTAGGGGCGGCTGCG
CTGGGCGGGGACCCAGGGCCCTCGGTGGGAGCCATGCCGTCTGCCGGACCCGGAGCCGAGGCATGTGCT
AGTTTCTTTATTTGTGTAACAAAAACCAAAAAACAAATGTTTATTTCTACGTTTCTTTAA
CCTTGATATAAATTATTCAGTAAGTGTGAGGTGAAACAAATGGAGTATTCTCGGATAGTTGCTATTTTG
TAAAGTTTCCGTGGCACTCGCTGTATGAAAGAGAGAGCAAAAGGGTGTCTGCGTCTGACCAAATC
GTAGCGTTTGTACAGAGGTTGTGCACTGTTTACAGAATCTTCTTTTATTCTCACTCGGGTTTCTCT
GTGGCTCCAGGCCAAAGTGCCGCTGAGACCCATGGCTGTGTTGGTGTGGCCATGGCTGTGTTGGTGGGACC
CGTGGCTGATGGTGTGGCTGTGGCTGTGCTGGGACTCGTGGCTGTCAATGGGACCTGTGGCTGTGCGT
GGGACCTACGTTGCTCGGTGGGACCCCTGTTATTGATGTGGCCCTGGCTGCCGGCACGGCCCGTGGCTGT
TGACGCACCTGTGGTTGTTAGTGGGGCCTGAGGTATCGGCGTGCCCAAGGCCGGCAGGTCAACCTCGCG
CTTGCTGGCCAGTCCACCCCTGCCTGCCGTGTGCTTCTCCTGCCCAGAACGCCCGTCCGCTCGCG
TCCACTGTGCTTTCAGAAAGTGCCCTTCTGCTGCGCAGATTCTCCCATCCTGGGACGGCGGAGTATTGAA
GCTCGTGACAAGTGCCCTCACACAGACCCCTCGCAACTGTCCACGCGTGCCGTGGCACCAGGCGCTGCC
ACCTGCCGGCCCCGGCCGCCCTCCTCGTGAAAGTGCAATTTTTGTAAATGTGTACATATTAAAGGAAGCA
CTCTGTATATTGATTGAATAATGCCACCAAAAAAAAAAAAAAAAAAATTCCTGCC

Figure 7

TCGAGGCGGCGATGCGGGCACGCGGCTGGGGACGCCTCGGCGGCTGCTGCTGCTACTGG
TTCTGTGCGTGACAGGCGACGCGGCCCATGGGCTATTTGAGCTGCAGCTGAGCGCGCTGCGGAA
CGTGAACGGGGAGCTGCTGAGCGGCGCCTGCTGTGACGCGACGCGCCGACGACGCGCGCGGG
GGGCTGCGGCCGCGACGAGTGCGACACGTACGTGCGCGTGTGCCTTAAGGAGTACCAGGCCAA
GGTGACGCCACGGGGCCCTGCAGCTACGGCTACGGGCCACGCCCGTGGTGGTGGCAACTC
CTTACTAGTGCCCGCGCGGCTGCGGGGACCGAGCGCGCGCGGTCTCGGACCGGCGG
CCACAGGACCCGGCCCTCGTCTGCTTCCCTTTTCAAGTTCGCTGGCCGCTTCTTTCACCCCTCA
TCGTGGAGGCTGGGACTGGGCAATGACACCACTCCAGATGAGGAGCTGCTGATTGAGCGGG
TGTGCGACGCTGGCATGATCAACCCGAGGACCGCTGGAAGAGCCTGCACCTCAGCGGCCACG
TGGCACACCTGGAGCTGCAGATCCGAGTGCGCTGTGATGAGAACTACTACAGTGCCACCTGCA
ACAAGTTCTGCCGGCCCCGCAACGACTTCTTTGGCCACTATACCTGCGACCACTACGGCAACAA
GGCCTGCATGGATGGCTGGATGGGCAAGAATGCAAGAAGCCGTGTGTAAACAAGGATGTAA
TTTGCTCCACGGGGGATGCACTGTGCTGGGGAGTGACAGGTGCAGCTACGGCTGGCAGGGCAA

GTTCTGTGACGAGTGTGTCCCTACCTGGCTGCGTGGCATGGCAGCTGTGTGGAGCCCTGGCAC
TGTGACTGTGAGACCAACTGGGGTGGCCTGCTCTGCGACAAAGACCTGAACACTGTGGCAGC
CACCACCCCTGTGTCAACGGGGTACCTGCATCAATGCTGAGCCTGACCAATACCTCTGCGCCT
GCCCAGATGGCTACTTGGGCAAGAACTGTGAGCGGGCTGAGCACGCCTGTGCCTCCAACCCGT
GTGCCAATGGGGCTCTTGCCACGAAGTGCCATCTGGCTTTGAATGCCACTGTCCGTCAGGATG
GAGCGGACCCACCTGTGCGCTCGACATTGATGAGTGTGCCTCTAACCCATGTGCAGCGGGTGGT
ACCTGCGTGGATCAGGTGGACGGCTTCGAGTGCATCTGCCCAGGAGCAGTGGGTGGGGGCTACT
TGCCAGCTGGACGCCAATGAGTGTGAAGGGAAGCCGTGCCTTAATGCTTTTTCTTGCAAAACC
TGATTGGCGGCTATTACTGTGATTGCCCTCCCGGGCTGGAAGGGCATCAACTGCCAAATCAACAT
CAACGATTGTCATGGGCAGTGTGAGCATGGGGGCACCTGCAAGGACCTGGTCAATGGGTACCA
GTGTGTGTGCCCGCGGGGCTTTGGAGGTGCGCATTGCGAACTAGAGTACGACAAGTGTGCCAG
CAGCCCTGCCCGCGGGGTGGCATCTGCGAGGACCTGGTGGATGGCTTCCGCTGCCACTGCCCA
CGGGGCTCTCTGGGCTGCACTGTGAGGTGGACATGGATCTCTGTGAACCAAGCCCCTGCCTCA
ACGGTGTCTGCTGCTACAACCTTGAGGGTGACTACTGCGCCTGCCCAGAAGACTTTGGTGG
CAAGAACTGCTCAGTGCCCAGGGACACATGCCCTGGCGGGGCATGTAGAGTGATCGATGGCTG
CGGGTTCGAGGCAGGGTCCAGGGGCACGCGGTGTGCGACCCCTCTGGTATATGTGGCCCTCACGG
GCACTGCGTTAGCCTGCCTGGGGGAACTTCTCCTGCATCTGTGACAGCGGCTTCACAGGCACC
TACTGCCATGAAAACATTGACGACTGCATGGGCCAGCCCTGCCGCAACGGGGGCACGTGCATT
GACGAAGTGGACTCCTTCCGCTGCTTCTGCCCCAGTGGCTGGGAAGGAGAACTCTGTGACATCA
ATCCCAACGACTGCCTCCCCGACCCCTGCCACAGCCGCGGCCGCTGCTATGACCTGGTCAATGA
CTTCTACTGTGCCTGTGACGATGGCTGGAAGGGCAAGACCTGCCACTCACGCGAGTTCAGTGT
GACGCCTACACCTGCAGCAACGGTGGCACATGCTATGACAGCGCGACACCTTCCGCTGCGCG
TGCCCTCCGGGCTGGAAGGGCAGCACCTGCACCATCGCCAAGACAGCAGCTGTGTGCCCAAT
CCCTGTGTGAATGGAGGCACCTGCGTGGGTAGCGGAGACTCTTCTCCTGCATCTGCCGGGATG
GCTGGGAGGGCCGACCTGCGACACATAACCAATGACTGCAACCCTCTGCCCTGCTATAACG
GAGGCATCTGTGTTGATGGCGTCAACTGGTTCCGCTGCGAGTGTGCGCCTGGCTTTGCGGGTCC
TGACTGCCGTATCAACATTGATGAGTGCCAGTCCCTCGCCCTGTGCCTACGGAGCCACGTGTGTG
GATGAGATCAACGGGTACCGCTGCAGCTGCCACCAGGTGCTTCTGGCCCCAGGTGCCAGGAA
GTGGTCATATTACGAGGCCCTGCTGGTCCCGGGGAATGTCCTTCCCGCATGGGAGTTCCTGGA
TGGAAGACTGCAACAGCTGCCGCTGCCTGGATGGCCACCGGATTGTAGCAAGGTATGGTGCG
GATGGAAGCCTTGCCCTGCTCTCTGGTCAGCCCAGCGATCCGAGTGCCAGTGGCCCCAGGGCA
GCAATGTCAGGAGAAGGCCGTGGGTGAGTGTGTCAGCCACCCTGTGAGAACTGGGGGGAGTG
TACAGCGGAGGAGCCTCTGCCACCCAGCACCCCTGTGAGCCACGGAGCAGTCATTTGGACAA
CAACTGTGCCCGACTCACACTGCGCTTCAACCGTGATCAAGTGCCTCAGGGCACCAACCGTGGGC
GCTATCTGCTCTGGAATCCGAGCCTTGCTGCCACGAGGGCGGGCGGCACACGACCGCCTCCTCC
TGCTGCTTTGTGATCGAGCATCCTCGGGGGCCAGTGCTGTGGAGGTGGCTATGTCTTTCAGCCC
TGCAAGGGACCTGCCTGACAGCAGCCTGATCCAGAGCACAGCCCACGCCATCGTGGCTGCTAT
CACTCAGAGAGGAAATAGCTCACTGCTGCTGGCTGTCACCGAGGTCAAGGTGGAACAGTTGT
TATGGGTGGCTCTTCCACAGGTCTGTTGGTGCCCGTGCTGTGTCAGCGTGTTCAGTGTGCTGTGGC
TCGCTGTGTGGTTATCTGCGTATGGTGGACACGAAAGCGCAGGAAAGAACGTGAGAGGAGCC
GGCTACCACGGGATGAGAGCACCAACAACAGTGGGCCCCGCTCAATCCCATCCGCAACCCCA
TTGAGCGGCCAGGCGGCAGCGGTCTGGGAACTGGGGGCCACAAGGACATACTCTACCAAGTGCA
AAAATTACACCGCCGCCCGCAGGGCAGGCGAGGCACTGCCCGGGCCAGCTGGCCATGGGG
CTGGTGGGGAGGACGAGAGGATGAAGAGCTGAGCCGTGGAGATGGGGACTCCCCAGAGGCA
GAGAAGTTCATCTCACACAAGTTACCAAAGACCCAGCTGCTCCCTCGGAAGGCCAGCCTGCT
GGGCTCCAGGGCCCAAGTGGACAACCGCGCCGTGAGAAGTACCAAGGACGTGCGCCGTGCTG
CGAGGAGGTAGCCAGCCACCAGGCTGGCACCCAGAACCCTTGCTGGCACCCACGCTGCCTGCCG
GACCATAGGAGGCCAAGGCCGTGTGCATAGTTTCTTTATTTTGTGTAAAAAACAAAACCAAAAC
CAAAAAACAAATGTTTATTTTTTACGTTTCTTTAACCTTGTATAAATTATTCAACGGCTGTCAGG
CGAAAAACACGGAGTATTCTCGGATCATTGCTATTTTTGTAAAGTTTCCGCGTCCGCACGCAC
TGTGGCAGGAGAGCAGGGCGTGTGTATGTGTGTGTGTGTGTGTGTCTCACC

Figure 8

GAAGGCCATGGTCTCCCCACGGATGTCCGGGCTCCTCTCCAGACTGTGATCCTAGCGCTATTTTCCTC
CCCCAGACACGGCCCGCTGGCGTCTTTCGAGCTGCAGATCCACTCTTTCGGGCGGGGTCCAGGCCCTGGGG
CCCCGGGTCCCCCTGCAGCGCCCGGTCCCCTGCCGCTCTTCTTCAGAGTCTGCCTGAAGCCTGGGCT

CTCAGAGGAGGCCGCCGAGTCCCCGTGCGCCCTGGGCGGGCGCTGAGTGCGCGCGGACCGGTCTACACC
GAGCAGCCCGGAGCGCCCGCGCCTGATCTCCCACTGCCGACGGGCTCTTGCAAGTGCCCTTCCGGGACG
CCTGGCCTGGACCTTCTCTTTCATCATCGAAACCTGGAGAGAGGAGTTAGGAGACCAGATTGGAGGGCC
CGCCTGGAGCCTGCTGGCGCGCGTGGCTGGCAGGCGGGCGCTTGGCAGCCGGAGGCCCGTGGGCCCCGGG
ATTACAGCGCGCAGGCGCCTGGGAGCTGCGCTTCTCGTACCGCGCGCGCTGCGAGCCGCTGCCGTCCGGA
CCGCGTGACGCGCCTCTGCCGTCCGCGCAGCGCCCCCTCGCGGTGCGGTCCGGGACTGCGCCCCCTGCGC
ACCGCTCGAGGACGAATGTGAGGCGCCGCTGGTGTGCCGAGCAGGCTGCAGCCCTGAGCATGGCTTCTGT
GAACAGCCCGGTGAATGCCGATGCCTAGAGGGCTGGACTGGACCCCTCTGCACGGTCCCTGTCTCCACCA
GCAGCTGCCTCAGCCCCAGGGGCCCGTCTCTGCTACCACCGGATGCCCTGTCCCTGGGCCTGGGCCCTG
TGACGGGAACCCGTGTGCCAATGGAGGCAGCTGTAGTGAGACACCCAGGTCTTTGAATGCACCTGCCCG
CGTGGGTTCTACGGGCTGCGGTGTGAGGTGAGCGGGGTGACATGTGCAGATGGACCCTGCTTCAACGGCG
GCTTGTGTGTGCGGGGTGCAGACCCTGACTCTGCCTACATCTGCCACTGCCACCTGGTTTCCAAGGCTC
CAACTGTGAGAAGAGGGTGGACCGGTGCAGCCTGCAGCCATGCCGCAATGGCGGACTCTGCCTGGACCG
GGCCACGCCCTGCGCTGCCGCTGCCGCGCCGGCTTCGCGGGTCTCGCTGCGAGCAGCACTGGACGACT
GCGCGGGCCGCGCCTGCGCTAACGGCGGCACGTGTGTGAGGGCGGCGCGGCGCGACCGCTGCTCCTGCC
GCTGGGCTTCGGCGGCCGCGACTGCCGCGAGCGCGCGGACCCGTGCGCCGCGCGCCCCCTGTGCTCACGGC
GGCCGCTGTACGCCCACTTCTCCGGCTCGTCTGCGCTTGGCTCCCGCTACATGGGAGCGCGGTGTG
AGTTCCCAAGTGCACCCCGACGGCGCAAGCGCCTTGCCCGCGGCCCGCGGGCCTCAGGCCCGGGGACCC
TCAGCGCTACCTTTTGCTCCGGCTCTGGGACTGCTCGTGCCCGCGGGCGTGGCCGGCGCTGCGCTCTTG
CTGGTCCACGTGCGCCGCCGTGGCCACTCCCAGGATGCTGGGTCTCGCTTGGTGGCTGGGACCCCGGAGC
CGTCAGTCCACGCACTCCCGGATGCACTCAACAACCTAAGGACGCAGGAGGGTTCCGGGGATGGTCCGG
CTCGTCCGTAGATTGGAATCGCCCTGAAGATGTAGACCCTCAAGGGATTTATGTACATCTGCTCCTCC
ATCTACGCTCGGGAGGTAGCGACGCCCTTTTCCCCCGCTACACACTGGGCGCGCTGGGCGAGGCGAGC
ACCTGCTTTTCCCTACCCTTCCTCGATTCTGTCCGTGAAATGAATTGGGTAGAGTCTCTGGAAGGTTTT
AAGCCCATTTTCAGTTCTAACTTACTTTATCCTATTTTGCATCCCTCTTATCGTTTTGAGCTACCTGCC
ATCTTCTCTTT

Figure 9

AAACCGGAACGGGGCCCAACTTCTGGGGCCTGGAGAAGGGAAACGAAGTCCCCCGGTTTTCCCGAGGT
GCCTTCTCGGGCATCTTGGTTTTCGGCGGGACTTCGCAGGGCGGATATAAAGAACGGCGCCTTTGGGA
AGAGGCGGAGACCGGCTTTAAAGAAAGAAGTCTTGGTCTGCGGCTTGGGCGAGGCAAGGGCGAGGCAG
GGCGCTTCTGCGGACGCTCCCCGTGGCCCTACGATCCCCCGCGCGTCCGCGCTGTTCTAAGGAGAGAA
GTGGGGGCCCCCAGGCTCGCGCGTGGAGCGAAGCAGCATGGGCAGTCGGTGCGCGCTGGCCCTGGCGT
GCTCTCGGCTTGTGTGTGAGGTCTGGAGCTCTGGGGTGTTCGAACTGAAGCTGCAGGAGTTCGTCAAC
AAGAAGGGGCTGCTGGGGAACCGCAACTGCTGCCGCGGGGGCGCGGGGCCACCGCCGTGCGCCTGCCGA
CCTTCTTCCGCGTGTGCCTCAAGCACTACCAGGCCAGCGTGTCCCCGAGCCGCCCTGCACCTACCGCAG
CGCCGTACCCCCGTGCTGGGCGTCACTCCTTCACTGTGCCGACGGCGGGGGCGCCGACTCCGCGTTC
AGCAACCCCATCCGCTTCCCCCTTCGGCTTCACTGGCCGGGCACCTTCTCTCTGATTATTGAAGCTCTCC
ACACAGATTCTCTGATGACCTCGCAACAGAAAACCCAGAAAGACTCATCAGCCGCTGGCCACCCAGAG
GCACCTGACGGTGGGCGAGGAGTGGTCCCAGGACCTGCACAGCAGCGGCCGACGGACCTCAAGTACTC
TACCGCTTCTGTGTGACGAACACTACTACGAGAGGGGTGCTCCGTTTTCTGCCGTCCCCGGGACGATG
CCTTCGGCCACTTCACTGTGGGGAGCGTGGGGAGAAAGTGTGCAACCCTGGCTGGAAAGGGCCCTACTG
CACAGAGCCGATCTGCCTGCCTGGATGTGATGAGCAGCATGGATTTTGTGACAAACAGGGGAATGCAAG
TGCAGAGTGGGCTGGCAGGGCCGGTACTGTGACGAGTGTATCCGCTATCCAGGCTGTCTCCATGGCACT
GCCAGCAGCCCTGGCAGTGCAACTGCCAGGAAGGCTGGGGGGGCGCTTTTCTGCAACCAGGACCTGAAC
CTGCACACACCATAAGCCCTGCAAGAATGGAGCCACCTGCACCAACACGGGCCAGGGGAGCTACACTTC
TCTTGCCGGCCTGGGTACACAGGTGCCACCTGCGAGCTGGGGATTGACGAGTGTGACCCAGCCCTTGTA
AGAACGGAGGGAGCTGCACGGATCTCGAGAACAGCTACTCCTGTACCTGCCACCCCGCTTCTACGGCAA
AATCTGTGAATTGAGTGCCATGACCTGTGCGGACGGCCCTTGCTTTAACGGGGGTGGTGTCTCAGACAGC
CCCGATGGAGGGTACAGCTGCCGCTGCCCGGTGGGCTACTCCGGCTTCACTGTGAGAAGAAAATTGACT
ACTGCAGCTCTTACCCTGTTCTAATGGTGCCAAAGTGTGTGGACCTCGGTGATGCCTACCTGTGCCGCTG
CCAGGCCGGCTTCTCGGGGAGGCACTGTGACGCAACGTGGACACTGCGCCTCCTCCCGTGGCGCAAC
GGGGGCACCTGCCGGGATGGCGTGAACGACTTCTCTGCACTGCCGCGCTGGCTACACGGGCAGGAACT
GCAGTGCCCCCGTACGAGGTGCGAGCACGCACCCTGCCACAATGGGGCCACCTGCCACCAGAGGGGCA
CGGCTATGTGTGCAATGTGCCGAAGCTACGGGGGTCCCAACTGCCAGTTCTGCTCCCCGAGCTGCCC
CCGGGCCCCAGCGGTGGTGGACCTCACTGAGAAGCTAGAGGGCCAGGGCGGGCCATTCCCCTGGGTGGCG
TGTGCGCCGGGGTCTATCCTTGTCTCATGCTGCTGCTGGGCTGTGCCGCTGTGGTGGTCTGCGTCCGGCT
GAGGCTGCAGAAGCACCGGCCCCAGCCGACCCCTGCCGGGGGGAGACGGAGACCATGAACAACCTGGC
AACTGCCAGCGTGAGAAGGACATCTCAGTCAGCATCATCGGGGCCACGCAGATCAAGAACACCAACAA
AGGCGGACTTCCACGGGGACACAGCGCCGACAAGAATGGCTTCAAGGCCCGCTACCCAGCGGTGGACA
TAACCTCGTGACGACCTCAAGGGTGACGACACCGCCGTACGGGACGCGCACAGCAAGCGTGACACCAG

TGCCAGCCCCAGGGCTCCTCAGGGGAGGAGAAGGGGACCCGACCACACTCAGGGGTGGAGAAGCATCG
AAAGAAAAAGGCCGACTCGGGCTGTTCAACTTCAAAAAGACACCAAGTACCAGTCGGTGTACGTCATATC
CGAGGAGAAGGATGAGTGCGTCATAGCAACTGAGGTGTAAATGGAAGTGAGATGGCAAGACTCCCGTT
CTCTTAAATAAGTAAATTTCAAGGATATATGCCCCAACGAATGCTGCTGAAGAGGAGGGAGGCCTCGT
GGACTGCTGCTGAGAAACCGAGTTCAGACCGAGCAGGTTCTCCTCCTGAGGTCTCGACGCCTGCCGACA
GCCTGTCGCGGCCCGGCCCTGCGGCACTGCCCTCCGTGACGTCGCCGTTGCACTATGGACAGTTGCTC
TTAAGAGAATATATATTTAAATGGGTGAACTGAATTACGCCTAAGAAGCATGCACTGCCTGAGTGTATAT
TTTGGATTCTTATGAGCCAGTCTTTTCTTGAATTAGAAACACAAACACTGCCTTTATTGTCTTTTGGAT
ACGAAGATGTGCTTTTTCTAGATGGAAAAGATGTGTGTTATTTTTGGATTTGTAAAAATATTTTTTCATG
ATATCTGTAAAGCTTGAGTATTTTGTGATGTTTCGTTTTTATAATTTAAATTTTGGTAAATATGTACAAA
GGCACTTCGGGTCTATGTGACTATATTTTTTGTATATAAATGTATTTATGGAATATTGTGCCAATGTTA
TTTGAGTTTTTACTGTTTTGTTAATGAAGAAATTCCTTTTTAAATATTTTTCCAAAATAAATTTTATG
AGGAATTC

Figure 10

ATGGCGGCAGCGTCCCGGAGCGCCTCTGGCTGGGCGCTACTGCTGCTGGTGGCACTTTGGCAGCAGCGCG
CGGCCGGCTCCGGCGTCTTCCAGCTGCAGGAGTTCATCAACGAGCGCGCGTACTGGCCAGTGG
CGGCCTTGCGAGCCCGGCTGCCGACTTTCTCCGCGTCTGCCCTAAGCACTTCCAGGCGGTCTGCTCG
CCCGGACCCTGCACCTTCGGGACCGTCTCCACGCGCGTATTGGGCACCAACTCCTTCGCTGTCCGGGACG
ACAGTAGCGGCGGGGGGCGCAACCTCTCCAACGCTTCAATTTACCTGGCCGGGTACCTTCTCGCT
CATCATCGAAGCTTGGCACGCGCCAGGAGACGACCTGCGGCCAGAGGCCTTGCCACCAGATGCACTCATC
AGCAAGATCGCCATCCAGGGCTCCCTAGCTGTGGGTGAGAACTGGTTATTGGATGAGCAAACAGCACCC
TCACAAGGCTGCGCTACTCTTACCGGGTCACTGCACTGACAACACTACTATGGAGACAACTGCTCCCGCCT
GTGCAAGAAGCGCAATGACCACTTCGGCCACTATGTGTGCCAGCCAGATGGCAACTTGTCTGCTGCC
GGTTGGACTGGGAATATTGCCAACAGCCTATCTGTCTTTCGGGCTGTCATGAACAGAATGGCTACTGCA
GCAAGCCAGCAGAGTGCCTCTGCCGCCCAGGCTGGCAGGGCCGGCTGTGTAACGAATGCATCCCCACAA
TGGCTGTGCCACGGCACCTGCAGCACTCCCTGGCAATGTACTTGTGATGAGGGCTGGGGAGGCCTGTTT
TGTGACCAAGATCTCAACTACTGCACCCACCACTCCCCATGCAAGAATGGGGCAACGTGCTCCAACAGTG
GGCAGCGAAGCTACACCTGCACCTGTGCGCCAGGCTACACTGGTGTGGACTGTGAGCTGGAGCTCAGCGA
GTGTGACAGCAACCCCTGTGCGAATGGAGGCAGCTGTAAGGACCAGGAGGATGGCTACCACTGCCTGTGT
CCTCCGGGCTACTATGGCCTGCATTGTGAACACAGCACCTTGAGCTGCGCCGACTCCCCCTGCTTCAATG
GGGGTCTCTGCCGGGAGCGCAACAGGGGGCCAACTATGCTTGTGAATGTCCCCCAACTTCAACGGCTC
CAACTGCGAGAAGAAAGTGGACAGGTGCACCAAGCAACCCCTGTGCCAACGGGGACAGTGCCTGAACCA
GGTCCAAGCCGCATGTGCCGCTGCCGTCTGGATTACGGGCACCTACTGTGAACCTCACGTCAGCGACT
GTGCCCGTAACCCCTTGCGCCACGGTGGCACTTGCCATGACCTGGAGAATGGGCTCATGTGCACCTGCC
TGCCGGCTTCTCTGGCCGACGCTGTGAGGTGCGGACATCCATCGATGCCTGTGCCTCGAGTCCCTGCTTC
AACAGGGCCACCTGCTACACCGACCTCTCCACAGACACCTTTGTGTGCAACTGCCCTTATGGCTTTGTGG
GCAGCCGCTGCGAGTTCCCGTGGGCTTGGCGCCAGCTTCCCTGGGTGGCCGTCTCGCTGGGTGTGGG
GCTGGCAGTGCTGCTGGTACTGCTGGGCATGTTGGCAGTGGCTGTGCGGCAGCTGCGGCTTCGACGGCCG
GACGACGGCAGGGAAGCCATGAACAACCTGTGCGAGTCTCCAGAAGGACAACCTGATTCCTGCCGCC
AGCTTAAAAACAAACCAGAAGAAGGAGCTGGAAGTGGACTGTGGCCTGGACAAGTCCAACCTGTGGCA
ACAGCAAAACACACATTGGACTATAATCTGGCCCCAGGGCCCCTGGGGCGGGGGACCATGCCAGGAAG
TTTCCCCACAGTGACAAGAGCTTAGGAGAGAAGGCGCCACTGCGGTTACACAGTGAAAAGCCAGAGTGC
GGATATCAGCGATATGCTCCCCAGGGAAGTCCATGTACAGTCTGTGTGTTGATATCAGAGGAGAGGAA
TGAATGTGTCAATTGCCACGGAGGTATAA

Figure 11

CTCGCAGGCTAGGAACCCGAGGCCAAGAGCTGCAGCCAAAGTCACTTGGGTGCAGTGTACTCCCTCACTA
GCCGCTCGAGACCCTAGGATTTGCTCCAGGACACGTACTTAGAGCAGCCACCGCCAGTCGCCCTCACC
TGGATTACCTACCGAGGCATCGAGCAGCGGAGTTTTTGAGAAGGCGACAAGGGAGCAGCGTCCCGAGGG
AATCAGCTTTTCAGGAACCTCGGCTGGCAGACGGGACTTGGGGAGAGCGACATCCCTAACAAGCAGATT
GGAGTCCCGGAGTGGAGAGGACACCCCAAGGATGACGCCTGCGTCCCGGAGCGCCTGTCGCTGGGCGT
ACTGCTGCTGAGCGTACTGTGGCCGACGAGCGCGCTGCGGCTCCGGCATCTTCCAGTCTGCGCTGCAG
GAGTTCGTCAACCAAGCGGTATGCTGGCCAATGGGCAGTCTGCGAACCAGGCTGCCGGAACCTTCTTCC
GCATTTGCCTTAAGCACTTCCAGGCAACCTTCTCCGAGGGACCTGCACCTTTGGCAATGTCTCCACGCC
GGTATTGGGCACCAACTCCTTCGTCGTCAGGGACAAGAATAGCGGCAGTGGTCGCAACCCCTCTGCAGTTG
CCCTTCAATTTACCTGGCCGGGAACCTTCTCACTCAACATCCAAGCTTGGCACACACCGGGGAGACGACC
TGCGGCCAGAGACTTCGCCAGGAACTCTCTCATCAGCCAAATCATCATCCAAGGCTCTCTTGCTGTGGG

TAAGATTTGGCGAACAGACGAGCAAAATGACACCCTCACCAGACTGAGCTACTCTTACCGGGTCATCTGC
AGTGACAACTACTATGGAGAGAGCTGTTCTCGCCTATGCAAGAAGCGCGATGACCACTTCGGACATTATG
AGTGCCAGCCAGATGGCAGCCTGTCTGCCTGCCGGGTGGACTGGGAAGTACTGTGACCAGCCTATATG
TCTTTCTGGCTGTCATGAGCAGAATGGTTACTGCAGCAAGCCAGATGAGTGCATCTGCCGTCCAGGTTGG
CAGGGTGCCTGTGCAATGAATGTATCCCCACAATGGCTGTCTGCATGGCACCTGCAGCATCCCCTGGC
AGTGTGCCTGCGATGAGGGATGGGGAGGTCTGTTTGTGACCAAGATCTCAACTACTGTACTCACCCTC
TCCGTGCAAGAATGGATCAACGTGTTCCAAACAGTGGGCCAAAGGGTTATACCTGCACCTGTCTCCAGGC
TACACTGGTGAGCACTGTGAGCTGGGACTCAGCAAGTGTGCCAGCAACCCCTGTGCAATGGTGGCAGCT
GTAAGGACCAGGAGAATAGCTACCACTGCCTGTGTCCCCAGGCTACTATGGCCAGCACTGTGAGCATAG
TACCTTGACCTGTGCGGACTCACCTGCTTCAATGGGGGCTCTTGCCGGGAGCGCAACCAGGGGTCCAGT
TATGCCTGCGAATGCCCCCACTTTACCGGCTCTAACTGTGAGAAGAAAGTAGACAGGTGTACCAGCA
ACCCGTGTGCCAATGGAGGCCAGTGCCTGAACAGAGGTCCAAGCCGAACCTGCCGTGCCGGCCTGGATT
CACAGGCACCCACTGTGAATGCACATCAGCGATTGTGCCGAAGTCCCTGTGCCACGGGGGCCTTGC
CAGCATCTGGAGAATGGGCCTGTGTGCACCTGCCCGCTGGCTTCTCTGGCAGGCGCTGCGAGGTGCGGA
TAACCCACGATGCCTGTGCCTCCGGACCCTGCTTCAATGGGGCCACCTGCTACACTGGCCTCTCCCCAAA
CAACTTCGTCTGCAACTGTCTTATGGCTTTGTGGGCAGCCGCTGCGAGTTTCCCGTGGGCTTGCCACCC
AGCTTCCCTGGGTAGCTGTCTCGCTGGGCGTGGGGCTAGTGGTACTGCTGGTGTCTGCTGGTCAATGGTGG
TAGTGGCTGTGCGGCAGCTGCGGCTTCGGAGGCCCGATGACGAGAGCAGGGAAGCCATGAACAATCTGC
AGACTTCCAGAAGGACAACCTAATCCCTGCCGCCAGCTCAAAAACACAAACCAGAAGAAGGAGCTGGA
GTGGACTGTGGTCTGGACAAGTCCAATTGTGGCAAACTGCAGAACCACACATTGGACTACAATCTAGCCC
CGGGACTCCTAGGACGGGGCAGCATGCCTGGGAAGTATCCTCACAGTGACAAGAGCTTAGGAGAGAAGT
GCCACTTCGGTTACACAGTGAGAAGCCAGAGTGTGCAATATCAGCCATTTGCTCTCCAGGGACTCTATG
TACCAATCAGTGTGTTGATATCAGAAGAGAGGAACGAGTGTGTGATTGCCACAGAGGTATAAGGCAGA
GCCTACTCAGACACCCAGCTCCGGCCAGCAGCTGGGCCTTCCTTCTGCATTGTTTACATTGCATCCTGT
ATGGGACATCTTTAGTATGCACAGTGTCTGTCTGCGGAGGAGGAGGGAATGGCATGAACAGACG
TGAACCCGCCAAGAGTTGCACCGGCTCTGCACACCTCCAGGAGTCTGCCTGGCTTCAGATGGGCAGCCCC
GCCAAGGGAACAGAGTTGAGGAGTTAGAGGAGCATCAGTTGAGCTGATATCTAAGGTGCCTCTCGAACTT
GGACTTGCTCTGCCAACAGTGGTCATCATGGAGCTCTTGACTGTTCTCCAGAGAGTGGCAGTGGCCCTAG
TGGGTCTTGCGCTGCTGTAGCTCCTGTGGGCATCTGTATTTCCAAAGTGCCTTTGCCAGACTCCATCC
TCACAGCTGGGCCCCAAATGAGAAAGCAGAGAGGAGTGTGCAAAAGGATAGGCCTCCCGCAGGCAGAACG
CCTTGGAGTTTGGCATTAAGCAGGAGCTACTCTGCAGGTGAGGAAAGCCGAGGAGGGGACACGTGTGC
TCTGCCTCCAACCCAGCAGGTGGGGTGCCACCTGCAGCCTCTAGGCAAGAGTTGGTCTTCCCCTGGT
CCTGGTGCCTCTGGGCTCATGTGAACAGATGGGCTTAGGGCACGCCCTTTTGCAGCCAGGGGTACAGG
CCTCACTGGGGAGCTCAGGGCCTTCATGCTAAACTCCCAATAAGGGAGATGGGGGGAAGGGGGCTGTGC
CTAGGCCCTTCCCTCCCTCACACCCATTTTGGGCCCTTGAGCCTGGGCTCCACCAGTGCCCACTGTTGC
CCCGAGACCAACCTTGAAGCCGATTTTCAAAAATCAATAATATGAGGTTTTGTTTGTAGTTTATTTGG
AATCTAGTATTTTGATAATTTAAGAATCAGAAGCACTGGCCTTTCTACATTTTATAACATTATTTGTAT
ATAATGTGTATTTATAATATGAAACAGATGTGTACATAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

Figure 12

AAACCCACTCCACCTTACTACCAGACAACCTTAGCCAAACCATTTACCCAAATAAAGTATAGGC
GATAGAAATTGAAACCTGGCGCAATAGATATAGTACCGCAAGGGAAGATGAAAAATTATAAC
CAAGCATAATATAGCAAGGACTAACCCCTATACCTTCTGCATAATGAATTAAGTAACTAGAAATACT
TTGCAAGGAGAGTCAAAGCTAAGGCCCCGAAACCAGGCGAGCTACCTAAGAACAGCTAAAA
GAGCACACCCGTCTATGTAGCAAAATAGTGGGAAGATTTATAGGTAGAGGCGACAAACCTACC
GAGCCTGGTGATAGCTGGTTGTCCAAGATAGAATCTTAGTTCAACTTTAAATTTGCCACAGAA
CCCTCTAAATCCCCTTGTAATTTAACTGTTAGTCCAAAGAGGAACAGCTCTTTGGACACTAGG
AAAAAACCTTGTAGAGAGAGTGTGACCCCAATTCCACACTTTTCCACATGTTGGATGGCCTTGG
AGTGGTAGCCATAAGCATTTTTGAATTCAACTAAAACTGAAGGATCCTTGAGGACGGCAGT
ACCTGGCATACTACACAGTCAGCGTTCAACAAGTGTGTGCAAAAGGTACATTGGGGCAGCTGGG
GGCAGAGTGATCTGTGACAATATCCCTGTTTGGTGAGCCGGCAGCGGAGCTGTGCCAGCGT
TACCCAGACATCATGCGTTTCACTGGGCGAGGGTGCCCGAGAATGGATCCGAGAGTGTGAGCAC
CAATTCGCCACCAACCGCTGGAACCTGTACCACCCTGGACCGGGACCACACCGTCTTTGGCCGTG
TCATGCTCAGAAGTAGCCGAGAGGCAGCTTTTGTATATGCCATCTCATCAGCAGGGGTGATCCA
CGCTATTACTCGCGCCTGTAGCCAGGGTGAACCTGAGTGTGTGACGCTGTGACCCCTACACCCGT
GGCCGACACCATGACCAGCGTGGGACTTTTGAAGTGGGGTGGCTGCAGTGACAACATCCACTAC
GGTGTCCGTTTTTGCCAAGGCCTTCGTGGATGCCAAGGAGAAGAGGCTTAAGGATGCCCGGGCC
CTCATGAACTTACATAATAACCGCTGTGGTGCACGGCTGTGCGGCGGTTTGTCAAGCTGGAGT

GTAAGTGCCATGGCGTGAGTGGTTCCTGTACTCTGCGCACCTGCTGGCGTGCACTCTCAGATTT
CCGCCGCACAGGTGATTACCTGCGGCGACGCTATGATGGGGCTGTGCAGGTGATGGCCACCCA
AGATGGTGCCAACTTCACCGCAGCCCGCCAAGGCTATCGCCGTGCCACCCGGAGTGATCTTGTC
TACTTTGACAACTCTCCAGATTACTGTGTCTTGGACAAGGCTGCAGGTTCCCTAGGCACTGCAG
GCCGTGTCTGCAGCAAGACATCAAAAGGAACAGACGGTTGTGAAATCATGTGCTGTGGCCGAG
GGTACGACACAACCTCGAGTCACCCGTGTTACCCAGTGTGAGTGCAAATCCACTGGTGCTGTGC
TGTACGGTGCAAGGAATGCAGAAATACTGTGGACGTCCATACTTGCAAAGCCCCCAAGAAGGC
AGAGTGGCTGGACCAGACCTGAACACACAGATACCTCACTCATCCCTCCAATTCAAGCCTCTCA
ACTCAAAAGCACAAAGATCCTTGCAATGCACACCTTCCTCCACCCTCCACCCTGGGCTGCTACCGC
TTCTATTTAAGGATGTAGAGAGTAATCCATAGGGACCATGGTGTCTGGCTGGTTCCTTAGCCC
TGGAAGGAGTTGTCAGGGGATATAAGAACTGTGCAAGCTCCCTGATTTCCCGCTCTGGAGAT
TTGAAGGGAGAGTAGAAGAGATAGGGGGTCTTTAGAGTGAATGAGTTGACTAAAGTACGTA
GTTGAGGCTCCTTTTTTCTTTCTTTGCAACCAGCTTCCCGACACTTCTTGGTGTGCAAGAGGAAG
GGTACCTGTAGAGAGCTTCTTTTTGTTTCTACCTGGCCAAAGTTAGATGGGACAAAGATGAATG
GCATGTCCCTTCTCTGAAGTCCGTTTGAGCAGAACTACCTGGTACCCCGAAAAGAAATCTTAG
GCTACCACATTCTATTATTGAGAGCCTGAGATGTTAGCCATAGTGGACAAGGTTCCATTACAT
GCTCATATGTTTATAAACTGTGTTTTGTAGAAGAAAAGAAATCATAACAATACAAACACACATT
CATTCTCTCTTTTCTCTCTACCATTTCTAACCTGTATTGGACAGCACTGCCTCTTTTGCTTACTT
GCTGCCTGTTCAAACCTGAGGTGGAATGCAGTGGTCCCATGCTTAACAGATCATTAACACACC
TAGAACACTCCTAGGATAGATTAATGT

Figure 13

ACCGCAGGGGGCTCCCGGACCCTGACTCTGCAGCCGAACCGGCACGGTTTCGTGGGGACCCAG
GCTTGCAAAGTGACGGTCATTTTCTTTTCTTCTCCCTCTTGAGTCCTTCTGAGATGATGGCTCT
GGGCGCAGCGGGAGCTACCCGGGTCTTTGTGCGATGGTAGCGGGCTCTCGGCGGCCACCC
TCTGCTGGGAGTGAGCGCCACCTTGAACCTCGGTTCTCAATTCCAACGCTATCAAGAACCTGCCC
CCACCGCTGGGCGCGCTGCGGGGACCCAGGCTCTGCAGTCAGCGCCGCGCGGGAATCCTG
TACCCGGGCGGGAATAAGTACCAGACCATTGCAACTACCAGCCGTACCCGTGCGCAGAGGAC
GAGGAGTGCGGCACTGATGAGTACTGCGCTAGTCCCACCCGCGGAGGGGACGCAGGCGTGCAA
ATCTGTCTCGCTGCAGGAAGCGCCGAAAACGCTGCATGCGTCACGCTATGTGCTGCCCCGGGA
ATTACTGCAAAAATGGAATATGTGTGTCTTCTGATCAAAATCATTTCCGAGGAGAAATTGAGGA
AACCATCACTGAAAGCTTTGGTAATGATCATAGCACCTTGGATGGGTATTCCAGAAGAACCACC
TTGTCTTCAAAAATGTATCACACCAAAGGACAAGAAGGTTCTGTTTGTCTCCGGTCATCAGACT
GTGCCTCAGGATTGTGTTGTGCTAGACACTTCTGGTCCAAGATCTGTAAACCTGTCTGAAAGA
AGGTCAAGTGTGTACCAAGCATAGGAGAAAAGGCTCTCATGGACTAGAAATATTCCAGCGTTG
TACTGTGGAGAAGGTCTGTCTTGCCGATACAGAAAGATCACCATCAAGCCAGTAATTCTTCT
AGGCTTCACACTTGTGAGAGACACTAAACCAGCTATCCAAATGCAGTGAACCTCTTTTATATAA
TAGATGCTATGAAAACCTTTTATGACCTTCATCAACTCAATCCTAAGGATATACAAGTTCTGTG
GTTTCAGTTAAGCATTCCAATAACACCTTCCAAAAACCTGGAGTGTAAGAGCTTTGTTTCTTTAT
GGAACCTCCCTGTGATTGCAGTAAATTACTGTATTGTAAATTCTCAGTGTGGCACTTACCTGTAA
ATGCAATGAAACTTTTAATTATTTTTCTAAAGGTGCTGCACTGCCTATTTTTCTCTTGTATGTA
AATTTTTGTACACATTGATTGTTATCTTGACTGACAAATATTCTATATTGAACTGAAGTAAATCA
TTTCAGCTTATAGTTCTTAAAAGCATAACCCCTTACCCCATTTAATTCTAGAGTCTAGAACGCAA
GGATCTCTTGGAATGACAAATGATAGGTACCTAAAATGTAACATGAAAATACTAGCTTATTTTC
TGAAATGTACTATCTTAATGCTTAAATTATATTTCCCTTTAGGCTGTGATAGTTTTTGAAATAAA
ATTTAACATTTAATATCATGAAATGTTATAA

Figure 14

AGAAAGCGGGAGCCCGCGGCGAGCGTAGCGCAAGTCCGCTCCCTAGGCATCGCTGCGCTGGCA
GCGATTCGCTGTCTCTTGAGTCAGGGGACAACGCTTCGGGGCAACTGTGAGTGCAGCTGTG
GGGACCTCGATTCTCTCAGATCTCGAGGATTCCGTCCGGGGACGTCTCCTGATCCCTACTAA

AGCGCCTGCTAACTTTGAAAAGGAGCACTGTGTCCTGCAAAGTTTGACACATAAAGGATAGGA
AAAGAGAGGAGAGAGAAAAGCAACTGAGTTGAAGGAGAAGGAGCTGATGCGGGCCTCCTGATCA
ATTAAGAGGAGAGTTAAACCGCCGAGATCCCGGCGGGACCAAGGAGGTGCGGGGCAAGAAGG
AACGGAAGCGGTGCGATCCACAGGGCTGGGTTTTCTTGACCTTGGGTACGCCTCCTTGCGCA
GAAAGCGCCTCGCATTTGATTGCTTCCAGTTATTGCAGAACTTCCTGTCCTGGTGGAGAAGCGG
GTCTCGCTTGGGTTCCGCTAATTTCTGTCCTGAGGCGTGAGACTGAGTTCATAGGGTCCTGGGTC
CCCGAACCAGGAAGGGTTGAGGGAACACAATCTGCAAGCCCCGCGACCCAAGTGAGGGGGCCC
CGTGTGGGGTCTCCTCCCTCCCTTTGCATTCCACCCCTCCGGGCTTTGCGTCTTCTGGGGACCC
CCTCGCCGGGAGATGGCCGCGTTGATGCGGAGCAAGGATTTCGTCTGCTGCCTGCTCCTACTGG
CCGCGGTGCTGATGGTGGAGAGCTCACAGATCGGCAGTTCGCGGGCCAACTCAACTCCATCA
AGTCCTCTCTGGGCGGGGAGACGCTGGTCAGGCCGCCAATCGATCTGCGGGCATGTACCAAG
GACTGGCATTTCGGCGGCAGTAAGAAGGGCAAAAACCTGGGGCAGGCCTACCCTTGATGACAGTG
ATAAGGAGTGTGAAGTTGGGAGGTATTGCCACAGTCCCCACCAAGGATCATCGGCCTGCATGG
TGTGTCGGAGAAAAAGAAGCGCTGCCACCGAGATGGCATGTGCTGCCCCAGTACCCGCTGCA
ATAATGGCATCTGTATCCAGTTACTGAAAGCATCTTAACCCCTCACATCCCGCTCTGGATGG
TACTCGGCACAGAGATCGAAACCACGGTCATTACTCAAACCATGACTTGGGATGGCAGAATCT
AGGAAGACCACACACTAAGATGTCACATATAAAGGGCATGAAGGAGACCCCTGCCTACGATC
ATCAGACTGCATTGAAGGGTTTTGCTGTGCTCGTCATTTCTGGACCAAAATCTGCAAACAGTG
CTCCATCAGGGGGAAGTCTGTACCAAAACAACGCAAGAAGGGTTCTCATGGGCTGGAAATTTTC
CAGCGTTGCGACTGTGCGAAGGGCCTGTCTTGCAAAGTATGGAAAGATGCCACCTACTCCTCCA
AAGCCAGACTCCATGTGTGTCAGAAAATTTGATCACCATTGAGGAACATCATCAATTGCAGACT
GTGAAGTTGTGATTTAATGCATTATAGCATGGTGGAAAATAAGGTTTCAGATGCAGAAGAATG
GCTAAAATAAGAAACGTGATAAGAATATAGATGATCAGAAAAGGGAGAAAAGAAAACATGAA
CTGAATAGATTAGAATGGGTGACAAATGCAGTGCAGCCAGTGTTTCCATTATGCAACTTGTCTA
TGTAATAATGTACACATTTGTGAAAATGCTATTATTAAGAGAACAGCACACAGTGGAAT
TACTGATGAGTAGCATGTGACTTTCCAAGAGTTTAGGTTGTGCTGGAGGAGAGGTTTCCTTCAG
ATTGCTGATTGCTTATACAAATAACCTACATGCCAGATTTCTATTCAACGTTAGAGTTTAAACA
AATACTCCTAGAATAACTTGTTATACAATAGGTTCTAAAAATAAAATTGCTAAACAAGAAATGA
AAACATGGAGCATTGTTAATTTACAACAGAAAATTACCTTTTGATTTGTAACACTACTTCTGCTG
TTCAATCAAGAGTCTTGGTAGATAAGAAAAAATCAGTCAATATTTCCAAATAATTGCAAAAATA
ATGGCCAGTTGTTTAGGAAGGCCTTTAGGAAGACAAATAAATAACAAACAAACAGCCACAAAT
ACTTTTTTTTCAAAATTTTAGTTTTACCTGTAATTAATAAGAACTGATACAAGACAAAAACAGTT
CCTTCAGATTCTACGGAATGACAGTATATCTCTTTATCCTATGTGATTCTGCTCTGAATGCA
TTATATTTTCCAACTATACCCATAAATTGTGACTAGTAAATACTTACACAGAGCAGAAATTT
CACAGATGGCAAAAAAATTTAAAGATGTCCAATATATGTGGGAAAAGAGCTAACACAGAGATC
ATTATTTCTTAAAGATTGGCCATAACCTGTATTTTATAGATAATTAGATTGGTAAATACATGTATT
CATACATACTCTGTGGTAATAGAGACTTGAGCTGGATCTGTACTGCACTGGAGTAAGCAAGAA
AATTGGGAAAACCTTTTCGTTTTGTTTCAGTTTTTGGCAACACATAGATCATATGTCTGAGGCACA
AGTTGGCTGTTTCATCTTTGAAACCAGGGGATGCACAGTCTAAATGAATATCTGCATGGGATTG
CTATCATAATATTTACTATGCAGATGAATTCAGTGTGAGGTCTGTGTCCGTACTATCCTCAAAT
TATTTATTTTATAGTGCTGAGATCCTCAAATAATCTCAATTTCAGGAGGTTTCACAAAATGGACT
CCTGAAGTAGACAGAGTAGTGAGGTTTCATTGCCCTCTATAAGCTTCTGACTAGCCAATGGCAT
CATCCAATTTTCTTCCCAAACCTCTGCAGCATCTGCTTTATTGCCAAAGGGCTAGTTTCGGTTTT
CTGCAGCCATTGCGGTTAAAAAATATAAGTAGGATAACTTGTAACCTGCATATTGCTAATCT
ATAGACACCACAGTTTCTAAATCTTTGAAACCCTTTACTACTTTTTTTAAACTTAACTCAGTT
CTAAATACTTTGTCTGGAGCACAAAACAATAAAAGGTTATCTTATAGTCGTGACTTTAACTTT
TGTAGACCACAATTCATTTTTAGTTTTCTTTACTTAAATCCCATCTGCAGTCTCAAATTTAAGT
TCTCCAGTAGAGATTGAGTTTGAGCCTGTATATCTATTAATAAATTTCAACTTCCCATATATT
TACTAAGATGATTAAGACTTACATTTTCTGCACAGGTCTGCAAAAACAAAAATTATAAACTAGT
CCATCCAAGAACCAAAGTTTGTATAAACAGGTTGCTATAAGCTTGGTGAAATGAAAATGGAAC
ATTTCAATCAAACATTTTCTATATAACAATTATTATTTACAATTTGGTTTTCTGCAATATTTTTC
TTATGTCCACCCTTTTAAAAATTATTATTGAAGTAATTTATTTACAGGAAATGTTAATGAGATG
TATTTTCTTAGAGATATTTCTTACAGAAAGCTTTGTAGCAGAATATATTGTCAGCTATTGACT
TTGTAATTTAGGAAAAATGTATAATAAGATAAAATCTATTAATTTTCTCCTCTAAAAACTGA
ATTCAAAGC

Figure 15

15/41

ACACACAGGCGGCGGCTGCGGGCGCAGAGCGGAGATGCAGCGGCTTGGGGCCACCCTGCTGTG
CCTGCTGCTGGCGGGCGGCGGTCCCCACGGCCCCCGCGCCCGCTCCGACGGCGACCTCGGCTCCA
GTCAAGCCCCGGCCCGGCTCTCAGCTACCCGAGGAGGAGGCCACCCTCAATGAGATGTTCCGC
GAGGTTGAGGAACTGATGGAGGACACGCAGCACAAATTGCGCAGCGCGGTGGAAGAGATGGA
GGCAGAAGAAGCTGCTGCTAAAGCATCATCAGAAAGTGAACCTGGCAAACCTTACCTCCCAGCTA
TCACAATGAGACCAACACAGACACGAAGGTTGGAAATAATACCATCCATGTGCACCGAGAAAT
TCACAAGATAACCAACAACCAGACTGGACAAATGGTCTTTTCAGAGACAGTTATCACATCTGTG
GGAGACGAAGAAGGCAGAAGGAGGCCACGAGTGCATCATCGACGAGGACTGTGGGCCCAGCAT
GTACTGCCAGTTTGCCAGCTTCCAGTACACCTGCCAGCCATGCCGGGGCCAGAGGATGCTCTGC
ACCCGGGACAGTGAGTGCTGTGGAGACCAGCTGTGTGTCTGGGGTCACTGCACCAAAATGGCC
ACCAGGGGCAGCAATGGGACCATCTGTGACAACCAGAGGGACTGCCAGCCGGGGCTGTGCTGT
GCCTTCCAGAGAGGCCTGCTGTTCCCTGTGTGCACACCCCTGCCCGTGGAGGGCGAGCTTTGCC
ATGACCCCGCCAGCCGGCTTCTGGACCTCATCACCTGGGAGCTAGAGCCTGATGGAGCCTTGA
CCGATGCCCTTGTGCCAGTGGCCTCCTCTGCCACCCACAGCCACAGCCTGGTGTATGTGTGC
AAGCCGACCTTCGTGGGGAGCCGTGACCAAGATGGGGAGATCCTGCTGCCAGAGAGGTCCCC
GATGAGTATGAAGTTGGCAGCTTCATGGAGGAGGTGCGCCAGGAGCTGGAGGACCTGGAGAGG
AGCCTGACTGAAGAGATGGCGCTGGGGGAGCCTGCGGCTGCCGCCGCTGCACTGCTGGGAGGG
GAAGAGATTTAGATCTGGACCAGGCTGTGGGTAGATGTGCAATAGAAATAGCTAATTTATTTC
CCAGGTGTGTGCTTTAGGCGTGGGCTGACCAGGCTTCTTCTACATCTTCTTCCAGTAAGTTTC
CCCTCTGGCTTGACAGCATGAGGTGTTGTGCATTTGTTTCAGCTCCCCAGGCTGTTCTCCAGGCT
TCACAGTCTGGTGCTTGGGAGAGTCAGGCAGGGTTAACTGCAGGAGCAGTTTGCCACCCCTGT
CCAGATTATTGGCTGCTTTGCCTCTACCAGTTGGCAGACAGCCGTTTGTCTACATGGCTTTGAT
AATTGTTTGAGGGGAGGAGATGGAAACAATGTGGAGTCTCCCTCTGATTGGTTTGGGGAAATG
TGGAGAAGAGTGCCCTGCTTTGCAAACATCAACCTGGCAAAAATGCAACAAATGAATTTTCCA
CGCAGTTCTTTCCATGGGCATAGGTAAGCTGTGCCTTCAGCTGTTGCAGATGAAATGTTCTGTTC
ACCCTGCATTACATGTGTTTATTCATCCAGCAGTGTGCTCAGCTCCTACCTCTGTGCCAGGGCA
GCATTTTCATATCCAAGATCAATTCCCTCTCTCAGCACAGCCTGGGGAGGGGGTCAATTGTTCTCC
TCGTCCATCAGGGATCTCAGAGGCTCAGAGACTGCAAGCTGCTTGCCCAAGTCACACAGCTAGT
GAAGACCAGAGCAGTTTCATCTGGTTGTGACTCTAAGCTCAGTGCTCTCTCCACTACCCACAC
CAGCCTTGGTGCCACCAAAAGTGCTCCCCAAAAGGAAGGAGAATGGGATTTTCTTTTGAGGCA
TGCACATCTGGAATTAAGGTCAAACCTAATTCTCACATCCCTCTAAAAGTAACTACTGTTAGGA
ACAGCAGTGTTCTCACAGTGTGGGGCAGCCGTCCTTCTAATGAAGACAATGATATTGACACTGT
CCCTCTTTGGCAGTTGCATTAGTAACCTTGAAAGGTATATGACTGAGCGTAGCATACAGGTTAA
CCTGCAGAAACAGTACTTAGGTAATTGTAGGGCGAGGATTATAAATGAAATTTGCAAAATCAC
TTAGCAGCAACTGAAGACAATTATCAACCAGTGGAGAAAATCAAACCGAGCAGGGCTGTGTG
AAACATGGTTGTAATATGCGACTGCGAACAACCTGAACCTCTACGCCACTCCACAAATGATGTTTTC
AGGTGTCATGGACTGTTGCCACCATGTATTATCCAGAGTTCTTAAAGTTTAAAGTTGCACATG
ATTGTATAAGCATGCTTTCTTTGAGTTTAAATTATGTATAAACATAAGTTGCATTTAGAAATCA
AGCATAAATCACTTCAACTGCTCTTCT

Figure 16

GACAAACAGACGACGTGCTGAGCTGCCAGCTTAGTGGAAGCTCTGCTCTGGGTGGAGAGCAGC
CTCGCTTTGGTGACGCACAGTGCTGGGACCCTCCAGGAGCCCCGGGATTGAAGGATGGTGGCG
GCCGTCTGCTGGGGCTGAGCTGGCTCTGCTCTCCCCTGGGAGCTCTGGTCTTGACTTCAACA
ACATCAGGAGCTCTGCTGACCTGCATGGGGCCCGGAAGGGCTCACAGTGCTGTCTGACACGG
ACTGCAATACCAGAAAGTTCTGCCTCCAGCCCCGCGATGAGAAGCCGTTCTGTGTACATGTCG
TGGGTTGCGGAGGAGGTGCCAGCGAGATGCCATGTGCTGCCCTGGGACACTCTGTGTGAACGA
TGTTTGTACTACGATGGAAGATGCAACCCCAATATTAGAAAGGCAGCTTGATGAGCAAGATGG
CACACATGCAGAAGGAACAACCTGGGCACCCAGTCCAGGAAAACCAACCCAAAAGGAAGCCAA
GTATTAAGAAATCACAAGGCAGGAAGGGACAAGAGGGAGAAAGTTGTCTGAGAACTTTTGACT
GTGGCCCTGGACTTTGCTGTGCTCGTCATTTTTGGACGAAAATTTGTAAGCCAGTCCTTTTGAG
GGACAGGTCTGCTCCAGAAGAGGGCATAAAGACACTGCTCAAGCTCCAGAAATCTTCCAGCGT

TGCGACTGTGGCCCTGGACTACTGTGTCGAAGCCAATTGACCAGCAATCGGCAGCATGCTCGAT
TAAGAGTATGCCAAAAAATAGAAAAGCTATAAATATTTCAAATAAAGAAGAATCCACATTGC
ATTTGAG

Figure 17

ATGGGGCTCTGGGCGCTGTTGCCTGGCTGGGTTTCTGCTACGCTGCTGCTGGGCGCTGGCCGCTCT
GCCCCAGCCCTGGCTGCCAACAGCAGTGGCCGATGGTGGGGTATTGTGAACGTAGCCTCCTCC
ACGAACCTGCTTACAGACTCCAAGAGTCTGCAACTGGTACTCGAGCCCAGTCTGCAGCTGTTGA
GCCGCAAACAGCGGCGCCTGATACGCCAAAATCCGGGGATCCTGCACAGCGTGAGTGGGGGGC
TGCAGAGTCCCGTGCGCGAGTGCAAGTGGCAGTTCCGGAATCGCCGCTGGAACGTGTTCACTG
CTCCAGGGCCCCACCTCTTCGGCAAGATCGTCAACCGAGGCTGTGAGAAACGGCGTTTATCTT
CGCTATCACCTCCGCCGGGGTACCCATTCCGGTGGCGCGCTCCTGCTCAGAAGGTTCCATCGAA
TCCTGCACGTGTGACTACCGGCGGCGCGGCCCGGGGGCCCCGACTGGCACTGGGGGGGCTGC
AGCGACAACATTGACTTCGGCCGCCTCTTCGGCCGGGAGTTTCGTGGACTCCGGGGAGAAAGGGG
CGGGACCTGCGCTTCTCATGAACCTTCACAACAACGAGGCAGGCCGTACGACCGTATTCTCCG
AGATGCGCCAGGAGTGCAAGTGCCACGGGATGTCCGGCTCATGCACGGTGCGCACGTGCTGGA
TGCGGCTGCCACGCTGCGCGCCGTGGGCGATGTGCTGCGCGACCGCTTCGACGGCGCCTCGCG
CGTCTGTACGGCAACCGCGGCAGCAACCGCGCTTCGCGAGCGGAGCTGCTGCGCCTGGAGCC
GGAAGACCCGGCCACAAACCGCCCTCCCCCAGCACCTCGTCTACTTCGAGAAATCGCCCAAC
TTCTGCACGTACAGCGGACGCTGGGCACAGCAGGCACGGCAGGGCGCGCCTGTAACAGCTCG
TCGCCCCGCGCTGGACGGCTGCGAGCTGCTCTGCTGCGGCAGGGGCCACCGCACGCGCACGCAG
CGCGTACCGAGCGCTGCAACTGCACCTTCCACTGGTGTGCTGCCACGTCAGCTGCCGCAACTGCA
CGCACACGCGCGTACTGCACGAGTGTCTGTGA

Figure 18

AGCAGAGCGGACGGGGCGCGCGGGAGGCGCGCAGAGCTTTCGGGCTGCAGGCGCTCGCTGCCGC
TGGGGAATTGGGCTGTGGGCGAGGCGGTCCGGGCTGGCCTTTATCGCTCGCTGGGCCCATCGTT
TGAAACTTTATCAGCGAGTCGCCACTCGTCGCAGGACCGAGCGGGGGGCGGGGGCGCGGCGAG
GCGGCGGCCGTGACGAGGCGCTCCCGGAGCTGAGCGCTTCTGCTCTGGGCACGCATGGCGCCC
GCACACGGAGTCTGACCTGATGCAGACGCAAGGGGGTTAATATGAACGCCCTCTCGGTGGAA
TCTGGCTCTGGCTCCCTCTGCTCTTGACCTGGCTCACCCCCGAGGTCAACTCTTCATGGTGTTAC
ATGAGAGCTACAGGTGGCTCCTCCAGGGTGTGTGCGATAATGTGCCAGGCCTGGTGAGCAGC
CAGCGGCAGCTGTGTACCGACATCCAGATGTGATGCGTGCCATTAGCCAGGGCGTGCCGAG
TGGACAGCAGAATGCCAGCACCAAGTTCGCGCAGCACCGCTGGAATTGCAACACCCTGGACAGG
GATCACAGCCTTTTTTGGCAGGGTCTACTCCGAAGTAGTCGGGAATCTGCCTTTGTTTATGCCAT
CTCCTCAGCTGGAGTTGTATTTGCCATCACCAGGGCCTGTAGCCAAGGAGAAGTAAAATCCTGT
TCCTGTGATCCAAAGAAGATGGGAAGCGCCAAGGACAGCAAAGGCATTTTTGATTGGGGTGGC
TGCAGTGATAACATTGACTATGGGATCAAATTTGCCCGCGCATTTGTGGATGCAAAGGAAAGG
AAAGGAAAGGATGCCAGAGCCCTGATGAATCTTCACAACAACAGAGCTGGCAGGAAGGCTGTA
AAGCGGTTCTTGAAACAAGAGTGCAAGTGCCACGGGGTGAGCGGCTCATGTACTCTCAGGACA
TGCTGGCTGGCCATGGCCGACTTCAGGAAAACGGGCGATTATCTCTGGAGGAAGTACAATGGG
GCCATCCAGGTGGTCATGAACCAGGATGGCACAGGTTTCACTGTGGCTAACGAGAGGTTTAAAG
AAGCCAACGAAAAATGACCTCGTGTATTTGAGAATTCTCCAGACTACTGTATCAGGGACCGAG
AGGCAGGCTCCCTGGGTACAGCAGGCCGTGTGTGCAACCTGACTTCCCGGGGCATGGACAGCT
GTGAAGTCATGTGCTGTGGGAGAGGCTACGACACCTCCCATGTACCCGGATGACCAAGTGTG
GGTGTAAGTTCCACTGGTGTGCGCCGTGCGCTGTGAGGACTGCCTGGAAGCTCTGGATGTGCA
CACATGCAAGGCCCCCAAGAACGCTGACTGGACAACCGCTACATGACCCAGCAGGCGTCACC
ATCCACCTTCCCTTCTACAAGGACTCCATTGGATCTGCAAGAACAACCTGGACCTTTGGGTTCTTTC
TGGGGGGATATTTCTAAGGCATGTGGCCTTTATCTCAACGGAAGCCCCCTTCTCCTCCCTGGG
GGCCCCAGGATGGGGGGCCACACGCTGCACCTAAAGCCTACCCTATTCTATCCATCTCCTGGTG
TTCTGCAGTCATCTCCCCTCCTGGCGAGTTCTCTTTGGAATAAGCATGACAGGCTGTTTCAGCCGG
GAGGGTGGTGGGCCCAGACCACTGTCTCCACCCACCTTGACGTTTCTTCTTCTAGAGCAGTTG

17/41

GCCAAGCAGAAAAAAGTGTCTCAAAGGAGCTTTCTCAATGTCTTCCCACAAATGGTCCCAAT
TAAGAAATTCCATACTTCTCTCAGATGGAACAGTAAAGAAAGCAGAATCAACTGCCCTGACTT
AACTTTAACTTTTGAAGACCAAGACTTTTGTCTGTACAAGTGGTTTTACAGCTACCACCCTTA
GGGTAATTGGTAATTACCTGGAGAAGAATGGCTTTCAATACCCTTTTAAGTTTAAAATGTGTAT
TTTTCAAGGCATTTATTGCCATATTAATCTGATGTAACAAGGTGGGGACGTGTGTCTTTGGT
ACTATGGTGTGTGTATCTTTGTAAGAGCAAAAGCCTCAGAAAGGGATTGCTTTGCATTACTGT
CCCCTTGATATAAAAAATCTTTAGGGAATGAGAGTTCCTTCTCACTTAGAATCTGAAGGGAATT
AAAAAGAAGATGAATGGTCTGGCAATATTCTGTAACCTATTGGGTGAATATGGTGGAAAAATAAT
TTAGTGGATGAATATCAGAAGTATATCTGTACAGATCAAGAAAAAAGGAAGAATAAAATTC
CTATATCAT

Figure 19

CGGGAGTCTTCGGGGAGCTATGCTGAGACCGGGTGGTGCGGAGGAAGCTGCGCAGCTCCCGCT
TCGGCGCGCCAGCGCCCCGGTCCCTGTGCCGTCGCCCGCGGCCCGGACGGCTCCCGGGCTTCG
GCCCCGCTAGGTCTTGCTGCTTCTGCTCCTGCTGCTGCTGACGCTGCCGGCCCCGCTAGACAC
GTCCTGGTGGTACATTGGGGCACTGGGGGCACGAGTGATCTGTGACAATATCCCTGGTTTGGTG
AGCCGGCAGCGGCAGCTGTGCCAGCGTTACCCAGACATCATGCGTTCAGTGGGCGAGGGTGCC
CGAGAATGGATCCGAGAGTGTGACACCAATTCCGCCACCACCGCTGGAAGTGTACCAACCTG
GACCGGGACCACACCGTCTTTGGCCGTGTCATGCTCAGAAGTAGCCGAGAGGCAGCTTTTGTAT
ATGCCATCTCATCAGCAGGGGTAGTCCACGCTATTACTCGCGCCTGTAGCCAGGGTGAAGTGA
TGTGTGACGCTGTGACCCCTACACCCGTGGCCGACACCATGACCAGCGTGGGGACTTTGACTGG
GGTGGCTGCAGTGACAACATCCACTACGGTGTCCGTTTTGCCAAGGCCTTCGTGGATGCCAAGG
AGAAGAGGCTTAAGGATGCCCGGGCCCTCATGAAGTTACATAATAACCGCTGTGGTTCGCACGG
CTGTGCGGCGGTTTCTGAAGCTGGAGTGTAAAGTGCCATGGCGTGAGTGGTTCCTGTACTCTGCG
CACCTGCTGGCGTGCACTCTCAGATTTCCGCCGCACAGGTGATTACCTGCGGCGACGCTATGAT
GGGGCTGTGCAGGTGATGGCCACCCAAGATGGTGCCAACCTCACCAGCCCCGCAAGGCTAT
CGCCGTGCCACCCGGACTGATCTTGTCTACTTTGACAACCTCTCCAGATTACTGTGTCTTGACAA
GGCTGCAGGTTCCCTAGGCACTGCAGGCCGTGTCTGCAGCAAGACATCAAAGGAACAGACGG
TTGTGAAATCATGTGCTGTGGCCGAGGGTACGACACAACCTCGAGTCACCCGTGTTACCCAGTGT
GAGTGCAAATCCACTGGTGTCTGTGCTGTACGGTGCAAGGAATGCAGAAATACTGTGGACGTC
CATACTTGCAAAGCCCCAAGAAGGCAGAGTGGCTGGACCAGACCTGAACACACAGATACCTC
ACTCATCCCTCCAATTCAAGCCTCTCAACTCAAAAGCACAAAGATCCTTGATGCACACCTTCCT
CCACCTCCACCTGGGCTGCTACCGCTTCTATTTAAGGATGTAGAGAGTAATCCATAGGGACC
ATGGTGTCTGGCTGGTTCCTTAGCCCTGGGAAGGAGTTGTCAGGGGATATAAGAACTGTGCA
AGCTCCCTGATTTCCCGCTCTGGAGATTTGAAGGGAGAGTAGAAGAGATAGGGGGTCTTTAGA
GTGAAATGAGTTGCACTAAAGTACGTAGTTGAGGCTCCTTTTTTCTTCTTGCACAGCTTCC
CGACACTTCTTGGTGTGCAAGAGGAAGGGTACCTGTAGAGAGCTTCTTTTTGTTTCTACCTGGC
CAAAGTTAGATGGGACAAAGATGAATGGCATGTCCCTTCTCTGAAGTCCGTTTGAGCAGAACTA
CCTGGTACCCCGAAAGAAAAATCTTAGGCTACCACATTCTATTATTGAGAGCCTGAGATGTTAG
CCATAGTGGAACAAGGTTCCATTACATGCTCATATGTTTATAAACTGTGTTTTGTAGAAGAAAA
AGAATCATAACAATACAAACACACATTCTCTCTTTTTCTCTCTACCATCTCAACCTGTAT
TGGACAGCACTGCCTCTTTTGCTTACTTGCTGCCTGTTCAAAGTGGAGGTGGAATGCAGTGGTTCC
CATGCTTAACAGATCATTAACACCCCTAGAACACTCCTAGGATAGATTAATGT

Figure 20

GCGCTTCTGACAAGCCCCGAAAGTCATTTCCAATCTCAAGTGGACTTTGTTCCAACCTATTGGGGG
CGTCGCTCCCCCTCYTCATGGTCGCGGGCAAACCTTCCTCCTCGGCGCCTCTTCTAATGGAGCCCC
ACCTGCTCGGGCTGCTCCTCGGCCTCCTGCTCGGTGGCACCAGGGTCCTCGCTGGCTACCCAAT
TTGGTGGTCCCTGGCCCTGGGCCAGCAGTACACATCTCTGGGCTCACAGCCCCTGCTCTGCGGC
TCCATCCCAGGCCTGGTCCCCAAGCAACTGCGCTTCTGCCGCAATTACATCGAGATCATGCCCG

CGTGGCCGAGGGCGTGAAGCTGGGCATCCAGGAGTGCCAGCACCAAGTTCCGGGGCCGCGCT
GGAAGTGCACCACCATAGATGACAGCCTGGCCATCTTTGGGCCCCTCCTCGACAAAGCCACCCG
CGAGTCGGCCTTCGTTACGCCATCGCCTCGGCCGGCGTGGCCTTCGCCGTACCCGCTCCTGC
GCCGAGGGCACCTCCACCATTTGCGGCTGTGACTCGCATCATAAGGGGGCCGCTGGCGAAGGC
TGGAAGTGGGGCGGCTGCAGCGAGGACGCTGACTTCGGCGTGTTAGTGTCCAGGGAGTTTCGG
GATGCGCGCGAGAACAGGCCGGACGCGCGCTCGGCCATGAACAAGCACAACAACGAGGGCGG
CCGCACGACTATCCTGGACCACATGCACCTCAAATGCAAGTGCCACGGGCTGTCCGGCAGCTGT
GAGGTGAAGACCTGCTGGTGGGCGCAGCCTGACTTCGGTGCCATCGGTGACTTCCTCAAGGACA
AGTATGACAGCGCCTCGGAGATGGTAGTAGAGAAGCACCGTGAGTCCCGAGGCTGGGTGGAGA
CCCTCCGGGCCAAGTACTCGCTCTTCAAGCCACCCACGGAGAGGGACCTGGTCTACTACGAGA
ACTCCCCCACTTTTGTGAGCCCAACCCAGAGACGGGTTCTTTGGCACAAGGGACCGGACTTG
CAATGTCACCTCCCACGGCATCGATGGCTGCGATCTGCTCTGCTGTGGCCGGGGCCACAACAG
AGGACGGAGAAGCGGAAGGAAAAATGCCACTGCATCTTCCACTGGTGCTGCTACGTCAGCTGC
CAGGAGTGTATTTCGCATCTACGACGTGCACACCTGCAAGTAGGGCACCAG

Figure 21

ATGAGTCCCCGCTCGTGCCTGCGTTTCGCTGCGCCTCCTCGTCTTCGCCGTCTTCTCAGCCGCCGC
GAGCAACTGGCTGTACCTGGCCAAGCTGTCTCGGTGGGGAGCATCTCAGAGGAGGAGACGTG
CGAGAAACTCAAGGGCCTGATCCAGAGGCAGGTGCAGATGTGCAAGCGGAACCTGGAAGTCAT
GGACTCGGTGCGCCGCGGTGCCAGCTGGCCATTGAGGAGTGCCAGTACCAAGTTCCGGAACCG
GCGCTGGAAGTGTCCACACTCGACTCCTTGCCCGTCTTCGGCAAGGTGGTGACGCAAGGGATT
CGGGAGGCGGCCTTGGTGTACGCCATCTCTTCGGCAGGTGTGGCCTTTGCAGTGACGCGGGCGT
GCAGCAGTGGGGAGCTGGAGAAGTGCGGCTGTGACAGGACAGTGTCATGGGGTCAGCCACAG
GGCTTCCAGTGGTCAGGATGCTCTGACAACATCGCCTACGGTGTGGCCTTCTCAAGTCGTTTG
TGGATGTGCGGGAGAGAAGCAAGGGGGCCTCGTCCAGCAGAGCCCTCATGAACCTCCACAACA
ATGAGGCCGGCAGGAAGGCCATCCTGACACACATGCGGGTGGAATGCAAGTGCCACGGGGTGT
CAGGCTCCTGTGAGGTAAAGACGTGCTGGCGAGCCGTGCCGCCCTTCCGCCAGGTGGGTACG
CACTGAAGGAGAAGTTTGATGGTGCCACTGAGGTGGAGCCACGCCGCGTGGGCTCCTCCAGGG
CACTGGTGCCACGCAACGCACAGTTCAAGCCGCACACAGATGAGGACTTGGTGTACTTGGAGC
CTAGCCCCGACTTCTGTGAGCAGGACATGCGCAGCGCGTGTGGGCACGAGGGCCGCACAT
GCAACAAGACGTCCAAGGCCATCGACGGCTGTGAGCTGCTGTGCTGTGGCCGCGGCTTCCACA
CGGCGCAGGTGGAGCTGGCTGAACGCTGCAGCTGCAAATTCCACTGGTGCTGCTTCGTCAAGTG
CCGGCAGTGCCAGCGGCTCGTGGAGTTGCACACGTGCCGATGA

Figure 22

ATTAATTCTGGCTCCACTTGTGCTCGGCCCAGGTTGGGGAGAGGACGGAGGGTGGCCGCAGC
GGGTTCTGAGTGAATTACCCAGGAGGGACTGAGCACAGCACCAACTAGAGAGGGGTGAGGGG
GTGCGGGACTCGAGCGAGCAGGAAGGAGGCAGCGCCTGGCACCAGGGCTTTGACTCAACAGA
ATTGAGACACGTTTGAATCGCTGGCGTGCCCCGCGCACAGGATCCCAGCGAAAATCAGATTC
CTGGTGAGGTTGCGTGGGTGGATTAATTTGGAAGAAAGAACTGCCTATATCTTGCCATCAAAA
ACTCACGGAGGAGAAGCGCAGTCAATCAACAGTAAACTTAAGAGACCCCCGATGCTCCCCTGG
TTTAACTTGTATGCTTGAAAATTATCTGAGAGGGAATAAACATCTTTCTTCTTCCCTCTCCAG
AAGTCCATTGGAATATTAAGCCCAGGAGTTGCTTTGGGGATGGCTGGAAGTGCAATGTCTTCCA
AGTTCTTCTAGTGGCTTTGGCCATATTTTTCTCCTTCGCCAGGTTGTAATTGAAGCCAATTCT
GGTGGTCGCTAGGTATGAATAACCTGTTTCAGATGTCAGAAGTATATATTATAGGACACAGCC
TCTCTGCAGCCAACTGGCAGGACTTTCTCAAGGACAGAAGAACTGTGCCACTGTATCAGGAC
CACATGCAGTACATCGGAGAAGGCGCGAAGACAGGCATCAAAGAATGCCAGTATCAATTCCGA
CATCGACGGTGGAACTGCAGCACTGTGGATAACACCTCTGTTTTTGGCAGGGTGATGCAGATAG
GCAGCCGCGAGACGGCCTTACATACGCCGTGAGCGCAGAGGGTGGTGAACGCCATGAGCC
GGCGTGGCCGAGGGCGAGCTGTCCACCTGCGGCTGCAGCCGCGCCGCGCGCCCCAAGGACC

TGCCGCGGGACTGGCTCTGGGGCGGCTGCGGCGACAACATCGACTATGGCTACCGCTTTGCCAA
GGAGTTCGTGGACGCCCCGCGAGCGGGAGCGCATCCACGCCAAGGGCTCCTACGAGAGTGCTCG
CATCCTCATGAACCTGCACAACAACGAGGCCGCGCAGGACGGTGTACAACCTGGCTGATGT
GGCCTGCAAGTGCCATGGGGTGTCCGGCTCATGTAGCCTGAAGACATGCTGGCTGCAGCTGGC
AGACTTCCGCAAGGTGGGTGATGCCCTGAAGGAGAAGTACGACAGCGCGGCGGCCATGCGGGCT
CAACAGCCGGGGCAAGTTGGTACAGGTCAACAGCCGCTTCAACTCGCCCACCACACAAGACCT
GGTCTACATCGACCCCAGCCCTGACTACTGCGTGCGCAATGAGAGCACC GGCTCGCTGGGCAC
GCAGGGCCGCCTGTGCAACAAGACGTGCGGAGGGCATGGATGGCTGCGAGCTCATGTGCTGCGG
CCGTGGGTACGACCAGTTCAAGACCGTGCAGACGGAGCGCTGCCACTGCAAGTCCACTGGTG
CTGCTACGTCAAGTGCAAGAAGTGCACGGAGATCGTGGACCAGTTTGTGTGCAAGTAGTGGGT
GCCACCCAGCACTCAGCCCCGCTCCAGGACCCGCTTATTTATAGAAAGTACAGTGATTCTGGT
TTTTGGTTTTTAGAAATATTTTTTATTTTTCCCCAAGAATTGCAACCGGAACCATTTTTTCTG
TTACCATCTAAGAACTCTGTGGTTTATTATTAATTATAATTATTATTGGCAATAATGGGGT
GGGAACCACGAAAAATATTTATTTGTGGATCTTTGAAAAGGTAATACAAGACTTCTTTTGAT
AGTATAGAATGAAGGGGGAAATAACACATACCCTAAGCTGTGTGGGACATGGTACACAT
CCAGATAAGTAAAGAAATACATTTTCTTTTCTCAAATATGCCATCATATGGGATGGGTAGGTTT
CAGTTGAAAGAGGGTGGTAGAAATCTATTCACAATTAGCTTCTATGACCAAAATGAGTTGTAA
ATTCTCTGGTGCAAGATAAAAGGTCTTGGGAAAAACAAAACAAAACAAAACCTCCCTTCC
CCAGCAGGGCTGCTAGCTTGCTTTCTGCATTTTCAAATGATAATTTACAATGGAAGGACAAGA
ATGTCATATTCTCAAGGAAAAAAGGTATATCACATGTCTCATTCTCCTCAAATATTCCATTTGCA
GACAGACCGTCATATTCTAATAGCTCATGAAATTTGGGCAGCAGGGAGGAAAGTCCCCAGAAA
TTAAAAAATTTAAACTCTTATGTCAAGATGTTGATTGAAAGCTGTTATAAGAATTGGGATTCC
AGATTTGTAAAAAGACCCCCAATGATTCTGGACACTAGATTTTTTGTGGGGAGGTTGGCTTG
AACATAAATGAAATATCCTGTATTTCTTAGGGATACTTGGTTAGTAAATTATAATAGTAGAAA
TAATACATGAATCCCATTCACAGGTTTCTCAGCCCAAGCAACAAGGTAATTGCGTGCCATTACAG
CACTGCACCAGAGCAGACAACCTATTTGAGGAAAAACAGTGAAATCCACCTTCCTCTTCACT
GAGCCCTCTCTGATTCCCTCCGTGTTGIGATGTGATGCTGGCCACGTTTCCAAACGGCAGCTCCAC
TGGGTCCCTTTGGTTGTAGGACAGGAAATGAAACATTAGGAGCTCTGCTTGGAAAACAGTTCA
CTACTTAGGGATTTTTGTTTTCTAAAACTTTTATTTTGAGGAGCAGTAGTTTTCTATGTTTTAATG
ACAGAACTTGGCTAATGGAATTCACAGAGGTGTTGCAGCGTATCACTGTTATGATCCTGTGTTT
AGATTATCCACTCATGCTTCTCCTATTGTACTGCAGGTGTACCTTAAAACGTGTTCCAGTGTACT
TGAACAGTTGCATTTATAAGGGGGGAAATGTGGTTTAAATGGTGCCTGATATCTCAAAGTCTTTT
GTACATAACATATATATATATACATATATATAAATATAAATATAAATATATCTCATTGCAGC
CAGTGATTTAGATTTACAGCTTACTCTGGGGTTATCTCTCTGTCTAGAGCATTGTTGTCCTTAC
TGCAGTCCAGTTGGGATTATTCCAAAAGTTTTTTGAGTCTTGAGCTTGGGCTGTGGCCCCGCTGT
GATCATACCCTGAGCACGACGAAGCAACCTCGTTTCTGAGGAAGAAGCTTGAGTTCTGACTCAC
TGAAATGCGTGTTGGGTTGAAGATATCTTTTTTCTTTTCTGCCTCACCCCTTTGTCTCCAACCTC
CATTTCTGTTCACTTTGTGGAGAGGGCATTACTTGTTTCGTTATAGACATGGACGTTAAGAGATAT
TCAAACTCAGAAGCATCAGCAATGTTTCTCTTTCTTAGTTTATTCTGCAGAATGGAAACCCAT
GCCTATTAGAAATGACAGTACTTATTAATTGAGTCCCTAAGGAATATTCAGCCCACTACATAGA
TAGCTTTTTTTTTTTTTTTTTTTTTTAATAAGGACACCTTTTCCAAACAGGCCATCAAATATGT
TCTTATCTCAGACTTACGTTGTTTTAAAGTTTGGAAAGATACACATCTTTTCATACCCCCCTT
AGGAGGTTGGGCTTTCATATCACCTCAGCCAACCTGTGGCTCTTAATTTATTGCATAATGATATCC
ACATCAGCCAACCTGTGGCTCTTTAATTTATTGCATAATGATATTCACATCCCTCAGTTGCAGTG
AATTGTGAGCAAAAAGATCTTGAAAGCAAAAAGCACTAATTAGTTTAAATGTCACTTTTTTGGT
TTTTATTATACAAAACCATGAAGTACTTTTTTTATTTGCTAAATCAGATTGTTCTTTTATGTGA
CTCATGTTTATGAAGAGAGTTGAGTTTAAACAATCCTAGCTTTTAAAGAAACTATTTAATGTAA
AATATTCTACATGTCATTCAGATATTATGTATATCTTCTAGCCTTTATTCTGTACTTTTAAATGTAC
ATATTTCTGTCTTGCGTGATTTGTATATTTCACTGGTTTAAAAACAAACATCGAAAGGCTTATT
CCAAATGGAAG

Figure 23

GGCAGGAGCGCAGGAGACACAGGCGCTGGCTGCCCCGTCCGCTCTCCGCTCCGCGCGCCCTCCTCGCC
CGGG ATGGGCCCCCGCGCGCGCGGATCCCTCGCTCCCGCGCGCGCGCTGCGCTCGCGCGCTCG
CACTGAAGCCCGGGCCCTCGCGCGCGCGGTTGCCCCGAGCCTCGCCCCCTGCCACCCGGGCGGCGG

20/41

TAGGGCGGTCACG ATGCTGCCGCCCTTACCCTCCCGCCTCGGGCTGCTGCTGCTGCTGCTCCTGTGCCCC
GCGCACGTCCGGCGGACTGTGGTGGGCTGTGGGCAGCCCCCTGGTTATGGACCCTACCAGCATCTGCAGGA
AGGCACGGCGGCTGGCCGGGCGGCAGGCCGAGTTGTGCCAGGCTGAGCCGGAAGTGGTGGCAGAGCTAGC
TCGGGGCGCCCGGCTCGGGGTGCGAGAGTGCCAGTTCCAGTTCCGCTTCCGCCGCTGGAATTGCTCCAGC
CACAGCAAGGCCCTTTGGACGCATCCTGCAACAGGACATTCCGGAGACGGCCTTCGTGTTCCGCATCACTG
CGGCCGGCGCCAGCCACGCCGTACGCAGGCCTGTTCTATGGGCGAGCTGCTGCAGTGGGCTGCCAGGC
GCCCCGCGGGCGGGCCCCCTCCCCGGCCCTCCGGCCTGCCGGCACCCCGGACCCCTGGCCCCGCGGGC
TCCCCGGAAGGCAGCGCCGCTGGGAGTGGGGAGGCTGCGGCGACGACGTGGACTTCGGGGACGAGAAGT
CGAGGCTCTTTATGGACGCGCGGCACAAGCGGGGACGCGGAGACATCCGCGCGTTGGTGCAACTGCACAA
CAACGAGGCGGGCAGGCTGGCCGTGCGGAGCCACACGCGACCCGAGTGCAAATGCCACGGGCTGTGCGGA
TCATGCGCGCTGCGCACCTGCTGGCAGAAGCTGCCTCCATTTGCGGAGGTGGGCGCGCGGCTGCTGGAGC
GCTTCCACGGCGCCTCACGCGTCATGGGCACCAACGACGGCAAGGCCCTGCTGCCCGCCGTCCGCACGCT
CAAGCCGCGGGCCGAGCGGACCTCCTCTACGCCGCGGATTGCCCCGACTTTTGCGCCCCCAACCGACGC
ACCGGCTCCCCCGGCACGCGCGGTGCGCCTGCAATAGCAGCGCCCCGACCTCAGCGGCTGCGACCTGC
TGTGCTGCGGCCGCGGGCACCGCCAGGAGAGCGTGACGCTCGAAGAGAACTGCCTGTGCCGCTTCCACTG
GTGCTGCGTAGTACAGTGCCACCGTTGCCGTGTGCGCAAGGAGCTCAGCCTCTGCCTGTGACCCGCCGCC
CGGCCGCTAGACTGACTTCGCGCAGCGGTGGCTCGCACCTGTGGGACCTCAGGGCACCGGCACCGGGCGC
CTCTCGCCGCTCGAGCCAGCCTCTCCCTGCCAAAGCCCAACTCCCAGGGCTCTGGAATGGTGAGGCGA
GGGGCTTGAGAGGAACGCCCCACCCAGGAAGGCCAGGGCGCCAGACGGCCCCGAAAAGGCGCTCGGGGAG
CGTTTAAAGGACACTGTACAGGCCCTCCCTCCCTTGGCCTCTAGGAGGAAACAGTTTTTTAGACTGGAA
AAAAGCCAGTCTAAAGGCCTCTGGATACTGGGCTCCCCAGAACTGCTGGCCACAGGATGGTGGGTGAGGT
TAGTATCAATAAAGATATTTAAACCAAAAAAAAAAAAAAAAAAAAAA

Figure 24

CACGCGTCCGGGCCAATCGGGACTATGAACCGGAAAGCGCTGCGCTGCCTGGGCCACCTCTTTC
TCAGCCTGGGCATGGTCTGCCTCCGGATCGGTGGCTTCTCCTCAGTGGTAGCTCTGGGCGCAAC
GATCATCTGTAACAAGATCCCAGGCCTGGCTCCCAGACAGCGGGCGATCTGCCAGAGCCGGCC
CGACGCCATCATCGTCATAGGAGAAGGCTCACAAATGGGCCTGGACGAGTGTAGTTTCAGTTC
CGCAATGGCCGCTGGAAGTGTCTGCACTGGGAGAGCGCACCGTCTTCGGGAAGGAGCTCAAA
GTGGGGAGCCGGGACGGTGCGTTCACCTACGCCATCATTGCCGCCGGCGTGGCCACGCCATC
ACAGCTGCCTGTACCCATGGCAACCTGAGCGACTGTGGCTGCGACAAAGAGAAGCAAGGCCAG
TACCACCGGGACGAGGGCTGGAAGTGGGGTGGCTGCTCTGCCGACATCCGCTACGGCATCGGC
TTCGCCAAGGTCTTTGTGGATGCCCCGGGAGATCAAGCAGAATGCCCGGACTCTCATGAACCTGC
ACAACAACGAGGCAGGCCGAAAGATCCTGGAGGAGAACATGAAGCTGGAATGTAAGTGCCAC
GGCGTGTGAGGCTCGTGCAACCACCAAGACGTGCTGGACCACACTGCCACAGTTTCGGGAGCTG
GGCTACGTGCTCAAGGACAAGTACAACGAGGCCGTTACGTGGAGCCTGTGCGTGCCAGCCGC
AACAAGCGGCCACCTTCTGAAGATCAAGAAGCCACTGTCGTACCGCAAGCCCATGGACACG
GACCTGGTGTACATCGAGAAGTCGCCCACTACTGCGAGGAGGACCCGGTGACCGGCAGTGTG
GGCACCAGGGCCGCGCCTGCAACAAGACGGCTCCCCAGGCCAGCGGCTGTGACCTCATGTGC
TGTGGGCGTGGCTACAACACCCACCACTACGCCCGCTGTGGCAGTGCAACTGTAAAGTTCCACT
GGTGTGCTATGTCAAGTGCAACACGTGCAGCGAGCGCACGGAGATGTACACGTGCAAGTGAG
CCCCGTGTGCACACCACCTCCCGCTGCAAGTCAAGTGTGCTGGGAGGACTGGACCGTTTCCAAG
CTGCGGGCTCCCTGGCAGGATGCTGAGCTGTCTTTTCTGCTGAGGAAGGTAATTTCTGTTCCACACCC
TCTGCGAGGATCCGTGGGGGAAAAAATCTCTCAGAACCTCAACTATTCTGTTCCACACCC
AATGTCTGCTCCACCTCCCCCAGACACAGCCCAAGTCCCTCCGCGGCTGGAGCGAAGCCTTCTG
CAGCAGGAACTCTGGACCCCTGGGCCTCATCACAGCAATATTTAACAATTTATTCTGATAAAAA
TAATATTAATTTATTTAATTAAGAAATTCTTCCACCTCAAAAAAAAAAAAAAAAAAAAAA
AAAAGGGGGG

Figure 25

21/41

TCGCTTACACACCAAGGAAAGTTGGGCTTTGAAGAATTCCATCCCCATGGCCACTGGAGGAA
GAATATTTTNCCTTCTTGTACCCATCTCCCCAGTTTTTTGGAATTTTCTCTAGCTGTTACTCC
AGAGGATTATGTTTTCTTCAAAGCCTTCTGTGTACATCTGTCTTTTACCTGTGTCTTCCAACTC
AGCCACAGCTGGTCCGTGAACAATTTCTGATGACTGGTCCAAAGGCTTACCTGATTTACTCCA
GCAGTGTGGCAGCTGGTGCCAGAGTGGTATTGAAGAATGCAAGTATCAGTTTGCCTGGGACC
GCTGGAACCTGCCCTGAGAGAGCCCTGCAGCTGTCCAGCCATGGTGGGCTTCGCAGTGCCAATCG
GGAGACAGCATTTGTGCATGCCATCAGTTCTGCTGGAGTCATGTACACCTGACTAGAAACTGC
AGCCTTGGAGATTTTGATAACTGTGGCTGTGATGACTCCCGCAACGGGCAACTGGGGGGACAA
GGCTGGCTGTGGGGAGGCTGCAGTGACAATGTGGGCTTCGGAGAGGGCGATTTCCAAGCAGTTT
GTCGATGCCCTGGAACAGGACAGGATGCACGGGCAGCCATGAACCTGCACAACAACGAGGCT
GGCCGCAAGGCGGTGAAGGGCACCATGAAACGCACGTGTAAGTGCCATGGCGTGTCTGGCAGC
TGACACACGCAGACCTGTTGGCTGCAGCTGCCCGAGTTCCGCGAGGTGGGCGCGCACCTGAAG
GAGAAGTACCACGCAGCACTCAAGGTGGACCTGCTGCAGGGTGTGGCAACAGCGCGGCGCCG
CGCGGCGCCATCGCCGACACCTTTCGCTCCATCTCTACCCGGGAGCTGGTGACCTGGAGGACT
CCCCGGACTACTGCCTGGAGAACAAAACGCTAGGGCTGCTGGGCACCGAAGGCCGAGAGTGCC
TAAGGCGCGGGCGGGCCCTGGGTGCTGGGAACCTCGCAGCTGCCGCGGGCTCTGCGGGGACT
GCGGGCTGGCGGTGGAGGAGCGCCGGCGGAGACCGTGTCCAGCTGCAACTGCAAGTTCCACT
GGTGTGTGCACTCCGCTGCGAGCAGTGCCGCGGAGGGTCAACCAAGTACTTCTGTAGCCGCG
AGAGCGGCGCGGGGGGGCGCTGCGCACAAACCCGGGAGAAAACCTAAGGGTTTCTCTGCC
CCCTCCTTTTCCCACTGGTTCTTGGCTTCTTTAGAGACCCCGTAATTGTGGAACCTAGGGAAT
GGGGAACCCGCTCTCCAGACCTAGGGATCCTGAAAGGGAAAACTGCAATTTCTCCAAAGCT
TGCCACTTTCCAGCCTGTTTCCCCAATTCTCTGTGCTCTCTAAAGCTCTGTCTGAATCCTCGC
AGCCACACCTAGGTCTGAAAACCTCAGGCTTTGAGTTACTGATCTTCTTGGATTAGGAAAACAG
GTGTTCTCTCTCCCTCTCTATCAGCCCTAATCTCTGACCTAGCCTATCAACCTTAGGCGCTG
GAAAAACCTTCTCATAACGCAGGACCCAGGTTAACTCAAAGCTTTGCCCTTTTGCCCACTGTC
TGCTACCAGGGGCTCACCTCTGCTGCACCTCTTCTGACAGCTCCTCCCCTGCTACTGCTGA
CCAAATTTCCAGGAATCTTGAATGCTTTCTCTCTCTTCTCCCTTTCTTTCCCAAAAAAACTG
AGGAAACTGGCCCCGAAAAGCATGTCTTTGGGGTTGGTTCCTAGAGGCAGAGGTGAAGATG
GAAGAGGGGAGCTCTGGAGTGCTAACTTGAACACCAAGGGTGCTACTCATCCCTATGGTATCATA
TCATGAATGGACTTTACTAGTGGGGCAATGACTTTCCTAGACAATAACCCGAGGGACTCCAGAT
ACATACCCCGAAGGTCTAGGAAATACGTTAAGGGCAGATTACAGTCATTTCTTACCTTTAAAG
GTAATTTCTCCCTTCTCTGACCTACTTCTCTAGCAACCAACTTTACCTCTTCTTCTCCAAAGG
ATCTTTGTTCTCTGAGCCAAGACTGAGGTAAATAAAGCCACTTTCTCTTACAGATCCTGGTCTG
CACCTCTAGA

Figure 26

GCGGCCGCGTCGACGGAGGGGCTGCAGCTCCGTCAGCCCGGCAGAGCCACCCTGAGCTCGGTG
AGAGCAAAGCCAGAGCCCCAGTCCTTTGCTCGCCGGCTTGCTATCTCTCTCGATCACTCCCTCC
CTTCTCTCCCTCCCTTCTTCCCGGCGGCCGCGCGGCGCTGGGGAAGCGGTGAAGAGGAGTGGCC
CGGCCCTGGAAGAATGCGGCTCTGACAAGGGGACAGAACCAGCGCAGTCTCCCCACGGTTTA
AGCAGCACTAGTGAAGCCCAGGCAACCCAACCGTGCCTGTCTCGGACCCCGCACCCAAACAC
TGGAGGTCTGATCGATCTGCCACCCGAGCCTCCGGGCTTCGACATGCTGGAGGAGCCCCGGC
CGCGGCCTCCGCCCTCGGGCTCGCGGGTCTCCTGTTCTGCGGTTGTGCAGTCGGGCTCTAAG
CAATGAGATTCTGGGCCTGAAGTTGCCTGGCGAGCCGCGCTGACGGCCAACACCGTGTGCTTG
ACGCTGTCCGGCCTGAGCAAGCGGCAGCTAGACCTGTGCCTGCGCAACCCCGACGTGACGGCG
TCCGCGCTTCAGGGTCTGCACATCGCGGTCCACGAGTGTACGACCAGCTGCGCGACCAGCGCT
GGAACCTGCTCCGCGCTTGAGGGCGGGCGGCCCTGCCGACCAACAGCGCCATCCTCAAGCGCG
GTTTCCGAGAAAGTGCTTTTCTTCTCCATGCTGGCTGTGGGTGCTGGAAGGGCAGTGGTAGCCAC
GGCCTGCAGCCTGGGCAAGCTGGTGAAGCTGTGGCTGTGGCTGGAAGGGCAGTGGTAGCAGGA
TCGGCTGAGGGCCAACTGCTGCAGCTGCAGGCACTGTCCCGAGGCAAGATTTCCCCACTCT
CTGCCAGCCCTGGCCCTGGCTCAAGCCCCAGCCCTGGCCCCAGGACACATGGGAATGGGGT
GGCTGTAACCATGACATGGACTTTGGAGAGAAGTTCTCTCGGGATTTCTTGGATTCCAGGGAAG
CTCCCCGGGACATCCAGGCACGAATGCGAATCCACAACAACAGGGTGGGGCGCCAGGTGGTAA
CTGAAAACCTGAAGCGGAAATGCAAGTGTGTCATGGCACATCAGGCAGCTGCCAGTTCAAGACAT

GCTGGAGGGCGGCCCCAGAGTTCCGGGCGAGTGGGGGCGGCGTTGAGGGAGCGGCTGGGCCGG
GCCATCTTCATTGATACCCACAACCGCAATTCTGGAGCCTTCCAGCCCCGTCTGCGTCCCCGTGCG
CCTCTCAGGAGAGCTGGTCTACTTTGAGAAGTCTCCTGACTTCTGTGAGCGAGACCCCACTATG
GGCTCCCCAGGGACAAGGGGCCGGGCTGCAACAAGACCAGCCGCCTGTTGGATGGCTGTGGC
AGCCTGTGCTGTGGCCGTGGGCACAACGTGCTCCGGCAGACACGAGTTGAGCGCTGCCATTGCC
GCTTCCACTGGTGCTGCTATGTGCTGTGTGATGAGTGCAAGGTTACAGAGTGGGTGAATGTGTG
TAAGTGAGGGTCAGCCTTACCTTGGGGCTGGGGAAGAGGACTGTGTGAGAGGGGCGCCTTTTC
AGCCCTTTGCTCTGATTTCCCTTCCAAGGTCACTCTTGGTCCCTGGAAGCTTAAAGTATCTACCTG
GAAACAGCTTTAGGGGTGGTGGGGGTGAGGTGGACTCTGGGATGTGTAGCCTTCTCCCCAACA
ATTGGAGGGTCTTGAGGGGAAGCTGCCACCCCTCTTCTGCTCCTTAGACACCTGAATGGACTAA
GATGAAATGCACTGTATTGCTCCTCCCACTTCTCAACTCCAGAGCCCCCTTAACCCCTGATTCTATA
CTCCTTTTGGCTGGGGAGTCCCTATAGTTTACCACCTCCTCTCCCTTGAGGGATAACCCAGGCA
CTGTTTGGAGCCATAAGATCTGTATCTAGAAAGAGATACCCCACTCCTATGTACTATCCCCAAA
CTCCTTTACTGCAGCCTGGGCTCCCTCTTGTGGGATAATGGGAGACAGTGGTAGAGAGGTTTTT
CTTGGGAAAGAGACAGAGTGCTGAGGGGCACCTCTCCCTGAATCCTCAGAGAGTTGTCTGTCCA
GGCCCTTAGGGAAGTTGTCTCCTTCCATTAGATGTTAATGGGGACCCTCCAAAGGAAGGGGT
TTCCCATGACTCTTGGAGCCTCTTTTCTTCTCAGCAGGAAGGGTGGGAAGGGATAATTTATC
ATACTGAGACTTGTCTTGGTTCCTGTTTGAACATAAAATAAATTAAGTTACTGGAATAAAAAA
AAAAA

Figure 27

TAACCCGCGCCTCCGCTCTCCCCGGCTGCAGGCGGCGTGCAGGACCAGCGGCGGCCGTGCAG
GCGGAGGACTTCGGCGCGGCTCCTCCTGGGTGTGACCCCGGGCGCGCCCGCGCGACGATG
AGGGCGCGGCCGAGGTCTGCGAGGCGCTGCTCTTCGCCCTGGCGCTCCAGACCGCGGTGTGCT
ATGGCATCAAGTGGCTGGCGCTGTCCAAGACACCATCGGCCCTGGCACTGAACAGACGCAAC
ACTGCAAGCAGCTGGAGGGTCTGGTGTCTGCACAGGTGCAGCTGTGCCGACGCAACCTGGAGC
TCATGCACACGGTGGTGCACGCCGCCGCGAGGTGATGAAGGCCTGTGCGCCGGCCTTTGCCGA
CATGCGCTGGAAGTGTCTCCTCCATTGAGCTCGCCCCAACTATTTGCTTGACCTGGAGAGAGGG
ACCCGGGAGTCGGCCTTCGTGTATGCGCTGTGCGGCCGCCACCATCAGCCACGCCATCGCCGGG
CCTGACCTCCGGGACCTGCCCGGCTGCTCCTGCGGCCCGTCCCAGGTGAGCCACCCGGGCC
CGGGAACCGCTGGGGAAGATGTGCGGACAACCTCAGCTACGGGCTCCTCATGGGGGCCAAGTT
TTCCGATGCTCCTATGAAGGTGAAAAAACAGGATCCCAAGCCAATAAACTGATGCGTCTACA
CAACAGTGAAGTGGGGAGACAGGCTCTGCGCGCCTCTCTGGAATGAAGTGTAAAGTGCCATGG
GGTGTCTGGCTCCTGCTCCATCCGCACCTGCTGGAAGGGGCTGCAGGAGCTGCAGGATGTGGCT
GCTGACCTCAAGACCCGATACCTGTGCGCCACCAAGGTAGTGACCGACCCATGGGCACCCGC
AAGCACCTGGTGCCCAAGGACCTGGATATCCGGCCTGTGAAGGACTGGGAAGTTGTTTATTTGC
AGAGCTCACCTGACTTTTGCATGAAGAATGAGAAGGTGGGCTCCCACGGGACACAAGACAGGC
AGTGCAACAAGACTTCCAACGGAAGCGACAGCTGCGACCTTATGTGCTGCGGGCGTGGCTACA
ACCCCTACACAGACCGCGTGGTTCGAGCGGTGCCACTGTAAGTACCACTGGTGTGCTACGTCAC
CTGCCGAGGTGTGAGCGTACCGTGGAGCGCTATGTCTGCAAGTGAGGCCCTGCCCTCCGCCCC
ACGCAGGAGCGAGGACTTTGCTCAAGGACCCTCAGCAACTGGGGCCGGGGGCTGGAGACACT
CCATGGAGCTCTGCTTGTGAATTCAGATGCCAGGCATGGGAGGCGGCTTGTGCTTTGCCTTCA
CTTGAAGCCACCAGGAACAGAAGGTCTGGCCACCCTGGAAGGAGNGCAGGACATCAAAGGA
GAGCGGGGCTTGGGATCGGTGAGACTGATACAGACTTGACCTTTACGGGCCACAGAGACCAGC
CTCCGGGAAGGGGTCTGCCCGCCTTCTCAGAATGTTCTGCGGGACCCCTGGCCACCCCTGGG
GTCTGAGCCTGTGGGCCACCACATGGAATCACTAGCTTCGGGTGTAAATGTTTCTTTTGT
NTTGCTTTTCTTCTTTTGGGATGTTGGAAGCTACAGAAATATTTATAAAATATATATATATATA
ATGATCTCTAATNTAAACTAGCTTTTAAAGCAGCTGTATGAAATAAATGCTGAGTGAGCCCCA
GCCCGCCCTGCAGTTCGCCGCTCGTCAAGTGAAGTGGCAGACCCTGGGGCTGGCAGAGGG
AGCTCTCAGTTTCCGGGCA

Figure 28

23/41

GGCGCGGCAAGATGCTGGATGGGTCCCCGCTGGCGCGCTGGCTGGCCGCGGCCTTCGGGCTGA
CGCTGCTGCTCGCCGCGCTGCGCCCTTCGGCCGCTACTTCGGGCTGACGGGCAGCGAGCCCT
GACCATCCTCCCGCTGACCCTGGAGCCAGAGCGGCGCCCGCCAGGCGCACTACAAGGCCTGCGA
CCGGCTGAAGCTGGAGCGGAAGCAGCGGCGCATGTGCCGCGGGACCCGGGCGTGGCAGAGA
CGCTGGTGGAGGCCGTGAGCATGAGTGCCTCGAGTGCCAGTTCCAGTTCCGCTTTGAGCGCTG
GAACTGCACGCTGGAGGGCCGCTACCGGGCCAGCCTGCTCAAGCGAGGCTTCAAGGAGACTGC
CTTCCTCTATGCCATCTCCTCGGCTGGCCTGACGCACGCACTGGCCAAGGCGTGCAGCGCGGGC
CGCATGGAGCGCTGTACCTGCGATGAGGCACCCGACCTGGAGAACCCTGAGGCCTGGCAGTGG
GGGGGCTGCGGAGACAACCTTAAGTACAGCAGCAAGTTTCGTCAAGGAATTCCTGGGCAGACGG
TCAAGCAAGGATCTGCGAGCCCGTGTGGACTTCCACAACAACCTCGTGGGTGTGAAGGTGATC
AAGGCTGGGGTGGAGACCACCTGCAAGTGCCACGGCGTGTGAGGCTCATGCACGGTGCAGGACC
TGCTGGCGGCAGTTGGCGCCTTTCATGAGGTGGGCAAGCATCTGAAGCACAAGTATGAGACG
GCACTCAAGGTGGGCAGCACCAACCAATGAAGCTGCCGGCGAGGCAGGTGCCATCTCCCCACCA
CGGGGCCGTGCGCTCGGGGGCAGGTGGCAGCGACCCGCTGCCCGCACTCCAGAGCTGGTGCAC
CTGGATGACTCGCCTAGCTTCTGCTGGCTGGCCGCTTCTCCCCGGGCACCGCTGGCCGTAGGT
GCCACCGTGAGAAGAACTGCGAGAGCATCTGCTGTGGCCGCGGCCATAACACACAGAGCCGGG
TGGTGACAAGGCCCTGCCAGTGCCAGGTGCGTTGGTGCTGCTATGTGGAGTGCAGGCAGTGCA
CGCAGCGTGAGGAGGTCTACACCTGCAAGGGCTGAGTTCCAGGCCCTGCCAGCCCTGCTGCA
CAGGGTGCAGGCATTGCACACGGTGTGAAGGGTCTACACCTGCACAGGCTGAGTTCTGGGCT
CGACCAGCCCAGCTGCGTGGGGTACAGGCATTGCACACAGTGTGAATGGGTCTACACCTGCAT
GGGCTGAGTCCCTGGGCTCAGACCTAGCAGCGTGGGGTAGTCCCTGGGCTCAGTCCTAGCTGCA
TGGGGTGCAGGCATTGCACAGAGCATGAATGGGCCTACACCTGCCAAGGCTGAATCCCTGGGC
CCAGCCAGCCCTGCTGCACATGGCACAGGCATTGCACACGGTGTGAGGAGTGTACACCTGCAA
GGGCTGAGGCCCTGGGCCCAGTCAGCCCTGCTGCTCAGAGTGCAGGCATTGCACATGGTGTGA
GAAGGTCTACACCTGCAAGGGACGAGTCCCCGGGCCTGGCCAACCCTGCTGTGCAGGGTGAGG
GCCATGCATGCTAGTATGAGGGGTCTACACCTGCAAGGACTGAGAGGGCTTTT

Figure 29

AGCCTGCAAAAACACAGAGGGCAAAGCCAGAAAGATGGAAAGGCACCCACCCATGCAGCTC
ACCACTTGCTCAGGGAGACCCTCTTCACAGGGGCTTCTCAAAAGACCTCCCTATGGTGGTTGG
GCATTGCCTCCTTCGGGGTTCCAGAGAAGCTGGGCTGCGCCAATTTGCCGCTGAACAGCCGCCA
GAAGGAGCTGTGCAAGAGGAAACCGTACCTGCTGCCGAGCATCCGAGAGGGCGCCCGGCTGGG
CATTACAGGAGTGCAGGAGCCAGTTCAGACACGAGAGATGGAAGTGCATGATCACCGCCGCCGC
CACTACCGCCCCGATGGGCGCCAGCCCCCTCTTTGGCTACGAGCTGAGCAGCGGCACCAAAGA
GACAGCATTTATTTATGCTGTGATGGCTGCAGGCCTGGTGCATTCTGTGACCAGGTGCATGAGT
GCAGGCAACATGACAGAGTGTTCCTGTGACACCACCTTGCAAGACGGCGGCTCAGCAAGTGAA
GGCTGGCACTGGGGGGGCTGCTCCGATGATGTCCAGTATGGCATGTGGTTCAGCAGAAAGTTCC
TAGATTTCCCATCGGAAACACCACGGGCAAAGAAAACAAAGTACTATTAGCAATGAACCTAC
ATAACAATGAAGCTGGAAGGCAGGCTGTGCGCAAGTTGATGTGATGAGTACTGCCGCTGCCACG
GAGTTTCGGCTCCTGTGCTGTGAAAACATGCTGGAACCATGTCTTCTTTTGAAGAGATTGG
CCATTTGTTGAAGGATAAATATGAAAACAGTATCCAGATATCAGACAAAATAAAGAGGAAAAT
GCGCAGGAGAGAAAAAGATCAGAGGAAAATACCAATCCATAAGGATGATCTGCTCTATGTTAA
TAAGTCTCCCAACTACTGTGTAGAAAGATAAGAACTGGGAATCCCAGGGACACAAGGCAGAGA
ATGCAACCGTACATCAGAGGGTGCAGATGGCTGCAACCTCCTCTGCTGTGGCCGAGGTTACAAC
ACCATGTGGTGCAGGCACGTGGAGAGGTGTGAGTGTAAAGTTCATCTGGTGTGCTATGTCCGTT
GCAGGAGGTGTGAAAGCATGACTGATGTCCACACTTGCAAGTAACCACTCCATCCAGCCTTGG
GCAAGATGCCTCAGCAATATACAATGGCATTGCAACCAGAGAGGTGCCCATCCCTGTGCAGCG
CTAGTAAAGTTGACTCTTGCAAGTGAATCCC

Figure 30

24/41

AGTTGAGGGATTGACACAAATGGTCAGGCGGCGGCGGCGGAGAAAGGAGGCGGAGGCGCAGGG
GGGAGCCGAGCCCGCTGGGCTGCGGAGAGTTGCGCTCTCTACGGGGCCGCGGCCACTAGCGCG
GCGCCGCCAGCCGGGAGCCAGCGAGCCGAGGGCCAGGAAGGCGGGACACGACCCCGGCGCGC
CCTAGCCACCCGGGTTCTCCCCGCCGCCGCGCTTCATGAATCGCAAGTTTCCGCGGCGGCGGC
GGCTGCGGTACGCAGAACAGGAGCCGGGGGAGCGGGCCGAAAGCGGCTTGGGCTCGACGGAG
GGCACCCGCGCAGAGGTCTCCCTGGCCGAGGGGGAGCCGCCGCCGCGGCGCTGCCCTGGCAGC
CCCAGCGGAGCGGCGCCAAGAGAGGAGCCGAGAAAGTATGGCTGAGGAGGAGGCGCCTAAGA
AGTCCCGGGCCGCGCGGTGGCGCGAGCTGGGAACTTTGTGCCGGGGCGCTCTCGGCCCGGC
TGGCGGAGGAGGGCAGCGGGGACGCCGGTGGCCGCCGCCGCCGCGCCAGTTGACCCCGGCGAT
TGGCGCGCCAGCTGCTGCTGCTGCTTTGGCTGCTGGAGGCTCCGCTGCTGCTGGGGGTCCGGGC
CCAGGCGGCGGGCCAGGGGCCAGGCCAGGGGGCCGGGGCGGGGCAGCAACCGCCGCCCGCGC
CTCAGCAGCAACAGAGCGGGCAGCAGTACAACGGCGAGCGGGGCATCTCCGTCCCGGACCACG
GCTATTGCCAGCCCATCTCCATCCCGCTGTGCACGGACATCGCGTACAACCAGACCATATGCC
CAACCTGCTGGGCCACACGAACCAGGAGGACGCGGGCCTGGAGGTGCACCAGTTCTACCTCT
AGTGAAAGTGCAGTGTTCCGCTGAGCTCAAGTTCTTCTGTGCTCCATGTACGCGCCGTGTGC
ACCGTGCTAGAGCAGGCGCTGCCGCCCTGCCGCTCCCTGTGCGAGCGCGCGCCAGGGCTGC
GAGGCGCTCATGAACAAGTTCGGCTTCCAGTGGCCAGACACGCTCAAGTGTGAGAAGTTCCCG
GTGCACGGCGCGCGGCGAGCTGTGCTGGGCCAGAACACGTCCGACAAGGGCACCCCGACGCCC
TCGCTGCTTCCAGAGTTCTGGACAGCAACCTCAGCACGGCGGCGGAGGGCACCGTGGCGGC
TTCGCGGGGGCGCGCGCGTCCGAGCGAGGCAAGTTCTCTGCCCGCGCGCCCTCAAGGTG
CCCTCCTACCTCAACTACCACTTCTGGGGGAGAAGGACTGCGGCGCACCTTGTGAGCCGACCA
AGGTGTATGGGCTCATGTACTTCGGGCCCGAGGAGCTGCGCTTCTCGCGCACCTGGATTGGCAT
TTGGTCAGTGCTGTGCTGCGCCTCCACGCTTTCACGGTGCTTACGTACCTGGTGGACATGCGG
CGCTTCAGCTACCCGAGCGGCCCATCATCTTCTTGTCGGGCTGTTACACGGCCGTGGCCGTGG
CCTACATCGCCGGCTTCTCTCTGGAAGACCGAGTGGTGTGTAATGACAAGTTCGCCGAGGACGG
GGCACGCACTGTGGCGCAGGGCACCAAGAAGGAGGGCTGCACCATCCTCTTCATGATGCTCTA
CTTCTTCAGCATGGCCAGCTCCATCTGGTGGGTGATCCTGTGCTCACCTGGTTCTGGCGGCTG
GCATGAAGTGGGGCCACGAGGCCATCGAAGCCAACCTCACAGTATTTTACCTGGCCGCTGGG
CTGTGCCGGCCATCAAGACCATCACCATCCTGGCGCTGGGCCAGGTGGACGGCGATGTGCTGA
GCGGAGTGTGCTTCGTGGGGCTTAACAACGTGGACGCGCTGCGTGGCTTCGTGCTGGCGCCCT
CTTCGTGTACCTGTTTATCGGCACGTCTTTCTGCTGGCCGGCTTTGTGTCGCTCTTCCGCATCCG
CACCATCATGAAGCACGATGGCACCAAGACCGAGAAGCTGGAGAAGCTCATGGTGCGCATTGG
CGTCTTCAGCGTGCTGTACACTGTGCCAGCCACCATCGTCATCGCCTGCTACTTCTACGAGCAG
GCCTTCCGGGACCAAGTGGGAACGCAGCTGGGTGGCCAGAGCTGCAAGAGCTACGCTATCCCC
TGCCCTCACCTCCAGGCGGGCGGAGGCGCCCCGCCGACCCGCCCATGAGCCCGACTTCACG
GTCTTCATGATTAAAGTACCTTATGACGCTGATCGTGCGGCATCACGTCGGGCTTCTGGATCTGGTC
CGGCAAGACCCTCAACTCCTGGAGGAAGTTATACAGAGGCTCACCAACAGCAAACAAGGGGA
GACTACAGCTCTGAGACCCGGGGCTCAGCCCATGCCAGGCCTCGGCCGGGGCGCAGCGATCCC
CCAAAGCCAGCGCCGTGGAGTTCGTGCCAATCCTGACATCTCGAGGTTTCTCACTAGACAACCT
CTCTTTTCGAGGCTCCTTTGAACAACCTCAGCTCCTGCAAAAGCTTCCGTCCCTGAGGCAAAAGG
ACACGAGGGCCCCGACTGCCAGAGGGAGGATGGACAGACCTCTTGCCCTCACACTCTGGTACCA
GGACTGTTGCTTTTATGATTGTAAATAGCCTGTGTAAGATTTTGTAAAGTATATTTGTATTTAA
ATGACGACCGATCACGCGTTTTTCTTTTTCAAAAGTTTTTAATTATTTAGGGCGGTTTAAACCATT
TGAGGCTTTTTCTTCTTGCCCTTTTCGGAGTATTGCAAAGGAGCTAAAACTGGTGTGCAACCGC
ACAGCGCTCCTGGTCGTCCTCGCGCGCCTCTCCCTACCACGGGTGCTCGGGACGGCTGGGCGCC
AGTCCGGGGCGAGTTCAGCACTGCGGGGTGCGACTAGGGCTGCGCTGCCAGGGTCACTTCCC
GCCTCCTCCTTTTGCCCCCTCCCCCTCCTTCTGTCCCCTCCCTTTCTTCTTCTGGCTTGAGGTAGGG
GCTCTTAAGGTACAGAACTCCACAAACCTTCCAAATCTGGAGGAGGGCCCCCATACTTACAAT
TCTCCTTGTCTCGGCGGTGGATTGCGAAGGCCCGTCCCTTCGACTTCTGAAGCTGGATTTTAA
ACTGTCCAGAACTTCTCCTCAACTTCATGGGGGCCACGGGTGTGGGCGCTGGCAGTCTCAGCC
TCCCTCCACGGTCACCTTCAACGCCAGACACTCCCTTCTCCACCTTAGTTGGTTACAGGGTGA
GTGAGATAACCAATGCCAAACTTTTTGAAGTCTAATTTTTGAGGGGTGAGCTCATTTTATTCTCT
AGTGTCTAAAACCTGGTATGGGTTTGGCCAGCGTCATGGAAAGATGTGGTTACTGAGATTTGGG
AAGAAGCATGAAGCTTTGTGTGGGTTGGAAGAGACTGAAGATATGGGTTATAAAATGTTAATT
CTAATTGCATACGGATGCCTGGCAACCTTGCCCTTGAGAATGAGACAGCCTGCGCTTAGATTTT
ACCGGTCTGTAAATGGAAATGTTGAGGTCACCTGGAAAGCTTTGTAAAGGAGTTGATGTTTGC

TTTCCTTAACAAGACAGCAAAACGTAAACAGAAATTGAAAACCTGAAGGATATTTTCAGTGTCAT
GGACTTCCTCAAAATGAAGTGCTATTTTCTTATTTTAAATCAAATAACTAGACATATATCAGAA
ACTTTAAATGTAAAAGTTGTACACTTTCAACATTTTATTACGATTATTATTCAGCAGCACATTC
TGAGGGGGGAACAATTCACACCACCAATAATAACCTGGTAAGATTTTCAGGAGGTAAAGAAGGT
GGAATAATTGACGGGGAGATAGCGCCTGAAATAAACAAAATATGGGCATGCATGCTAAAGGG
AAAATGTGTGCAGGTCTACTGCATTAAATCCTGTGTGCTCCTCTTTTGGATTTACAGAAATGTGT
CAAATGTAAATCTTTCAAAGCCATTTAAAAATATTCACCTTAGTTCTGTGAAGAAGAGGAGA
AAAGCAATCCTCCTGATTGTATTGTTTTAACTTTAAGAATTTATCAAATGCCGGTACTTAGG
ACCTAAATTTATCTATGTCTGTCATACGCTAAAATGATATTGGTCTTTGAATTTGGTATACATTT
ATTCTGTTCACTATCAGAAAATCATCTATTTTATAGAGGAATAGAAGTTTATATATATATAATA
CCATATTTTTAATTTACAAAATAAAAAATTCAAAGTTTTGTACAAAATTATATGGATTTTGTGCC
TGAAAATAATAGAGCTTGAGCTGTCTGAACTATTTTACATTTTATGGTGTCTCATAGCCAATCCC
ACAGTGTA AAAATTCA

Figure 31

CGAGTAAAGTTTGCAAAGAGGGCGCGGGAGGGCGGCAGCCGCAGCGAGGAGGGCGGGCGGGGAAGA
AGCGCAGTCTCCGGGTTGGGGGCGGGGGCGGGGGGGCGCCAAGGAGCCGGGTGGGGGGCGG
CGGCCAGCATGCGGCCCGCAGCGCCCTGCCCGCCTGCTGCTGCCGCTGCTGCTGCCGCGC
CGCCGGGCGCGCCAGTTCCACGGGGAGAAGGGCATCTCCATCCCGGACCACGGCTTCTGCCA
GCCCATCTCCATCCCGCTGTGCACGGACATCGCCTACAACCAGACCATCATGCCCAACCTTCTG
GGCCACACGAACCAGGAGGACGCAGGCCTAGAGGTGCACCAGTTCTATCCGCTGGTGAAGGTG
CAGTGCTCGCCCGAACTGCGCTTCTTCTGTGCTCCATGTACGCACCCGCTGTGCACCGTGCTGG
AACAGGCCATCCCGCCGTGCCGCTCTATCTGTGAGCGCGCGGCCAGGGCTGCGAAGCCCTCAT
GAACAAGTTCGGTTTTAGTGCCCCGAGCGCCTGCGCTGCGAGCACTTCCCGCGCCACGGCGCC
GAGCAGATCTGCGTCGGCCAGAACCACTCCGAGGACGGAGCTCCCGCGCTACTCACCACCGCG
CCGCCGCGGGGACTGCAGCCGGGTGCCGGGGGACCCCGGGTGGCCCCGGGCGGCGGGCGCT
CCCCGCGCTACGCCACGCTGGAGCACCCCTTCCACTGCCCGCGCTCCTCAAGTGGCCATCCT
ATCTCAGCTACAAGTTTCTGGGCGAGCGTGATTGTGCTGCGCCCTGCGAACCTGCGCGCCGA
TGGTTCATGTTCTTCTCACAGGAGGAGACGCGTTTCGCGCGCCTCTGGATCCTCACCTGGTCTG
GTGCTGTGCTGCGCTTCCACCTTCTTCACTGTCAACACGTACTTGGTAGACATGCAGCGCTTCCG
CTACCCAGAGCGGCCTATCATTTTTCTGTGCGGGCTGCTACACCATGGTGTGCGGTGGCCTACATC
GCGGGCTTCGTGCTCCAGGAGCGCGTGGTGTGCAACGAGCGCTTCTCCGAGGACGGTTACCGC
ACGGTGGTGCAGGGCACCAAGAAGGAGGGCTGCACCATCCTCTTCATGATGCTCTACTTCTTCA
GCATGGCCAGCTCCATCTGGTGGGTATCCTGTGCTCACTGGTTCCTGGCAGCCGGCATGAA
GTGGGGCCACGAGGCCATCGAGGCCAACTCTCAGTACTTCCACCTGGCCGCTGGGCCGTGCCG
GCCGTCAAGACCATACCATCCTGGCCATGGGCCAGATCGACGGCGACCTGCTGAGCGGCGTG
TGCTTCGTAGGCCTCAACAGCCTGGACCCGCTGCGGGGCTTCGTGCTAGCGCCGCTCTTCGTGT
ACCTGTTTCATCGGCACGTCTTCTCCTGGCCGGCTTCGTGTGCTCTTCCGCATCCGCACCATC
ATGAAGCACGACGGCACCAAGACCGAAAAGCTGGAGCGGCTCATGGTGCGCATCGGCGTCTTC
TCCGTGCTCTACACAGTGCCCGCCACCATCGTCATCGCTTGCTACTTCTACGAGCAGGCCTTCCG
CGAGCACTGGGAGCGCTCGTGGGTGAGCCAGCACTGCAAGAGCCTGGCCATCCCGTGCCCGGC
GCACTACACGCCGCGCATGTGCCCCGACTTCACGGTCTACATGATCAAATACCTCATGACGCTC
ATCGTGGGCATCACGTGCGGCTTCTGGATCTGGTGGGCAAGACGCTGCACTCGTGGAGGAAG
TTCTACACTCGCCTACCAACAGCCGACACGGTGAGACCACCGTGTGAGGGACGCCCCCAGGC
CGGAACCGCGCGGCGCTTCTCCTCCGCCCGGGTGGGGCCCCTACAGACTCCGTATTTTATTTTT
TAAATAAAAAACGATCGAAACATTTCACTTTTAGGTTGCTTTTTAAAGAGAACTCTCTGCC
AACACCCCC

Figure 32

GCCGCTCCGGGTACCTGAGGGACGCGCGGCCCGCCGCGGCAGGCGGTGCAGCCCCCCCCACC
CCTTGAGGCCAGGCGCCGGGTCTGAGGATAGCATTTCTCAAGACCTGACTTATGGAGCACTTG
TAACCTGAGATATTTCAAGTTGAAGGAAGAAATAGCTCTTCTCCTAAGATGGAATCTGTGGTTG

GGAATGTGGTTGATCAACTTGATATGTTGGCCAAATGTGCCCCATGTAATAAAATGAAAAGAA
GAGACAAGATGATGTCATTTTCCCATATTGTGAAACCAAAAACAAACGCCTTTTGTGAGACCAA
GCTAACAAACCTCTGACGGTGCGAAGAGTATTTAACTGTTTGAAGAATTTAACAGTAAGATACA
GAAGAAGTACCTTCGAGCTGAGACCTGCAGGTGTATAAATATCTAAAATACATATTGAATAGG
CCTGATCATCTGAATCTCCTTCAGACCCAGGAAGGATGGCTATGACTTGGATTGTCTTCTCTCTT
TGGCCCTTGACTGTGTTTCATGGGGCATATAGGTGGGCACAGTTTGTCTTGTGAACCTATTAC
CTTGAGGATGTGCCAAGATTTGCCTTATAATACTACCTTCATGCCTAATCTTCTGAATCATTATG
ACCAACAGACAGCAGCTTTGGCAATGGAGCCATTCCACCCTATGGTGAATCTGGATTGTTCTCG
GGATTTCCGGCCTTTTCTTTGTGCACTCTACGCTCCTATTTGTATGGAATATGGACGTGTCACAC
TTCCCTGTGCTAGGCTGTGTCAGCGGGCTTACAGTGAGTGTTTGAAGCTCATGGAGATGTTTGG
TGTTCTTGGCCTGAAGATATGGAATGCAGTAGGTTCCCAGATTGTGATGAGCCATATCCTCGA
CTTGTGGATCTGAATTTAGCTGGAGAACCAACTGAAGGAGCCCCAGTGGCAGTGCAGAGAGAC
TATGGTTTTTGGTGTCCCCGAGAGTTAAAAATTGATCCTGATCTGGGTTATTCTTTTCTGCATGT
GCGTGATTGTTACCTCCTTGTCCAAATATGTACTTCAGAAGAGAAGAACTGTCAATTTGCTCGCT
ATTTTCATAGGATTGATTTCAATCATTTCCTCTCGGCCACATTGTTTACTTTTTTAACITTTTTGA
TTGATGTCAAGATTCCGTTATCCTGAAAGGCCTATTATATTTATGCAGTCTGCTACATGATG
GTATCCTTAATTTTCTTCAATTGGATTTTTGTCTTGAAGATCGAGTAGCCTGCAATGCATCCATCCC
TGCACATATAAGGCTTCCACAGTGACACAAGGATCTCATAATAAAGCCTGTACCATGCTTTTT
ATGATACTCTATTTTTTTACTATGGCTGGCAGTGTATGGTGGGTAAATCTTACCATCACATGGTT
TTTAGCAGCTGTGCCAAAGTGGGGTAGTGAAGCTATTGAGAAGAAAGCATTGCTGTTTACGCC
AGTGCATGGGGCATCCCCGGAACCTCAACCATCATCCTTTTAGCGATGAATAAAATTGAAGGTG
ACAATATTAGTGGCGTGTGTTTTGTTGGCCTCTACGATGTTGATGCATTGAGATATTTTGTCTT
GCTCCCTCTGCCTGTATGTGGTAGTTGGGGTTTCTCTCCTCTTAGCTGGCATTATATCCCTAAA
CAGAGTTCGAATTGAGATTCCATTAGAAAAGGAGAACCAAGATAAATTAGTGAAGTTTATGAT
CCGGATCGGTGTTTTTCAGCATTCTTATCTCGTACCCTCTTGGTTGTAATTGGATGCTACTTTTA
TGAGCAAGCTTACCGGGGCATCTGGGAAACAACGTGGATACAAGAACGCTGCAGAGAATATCA
CATTCCATGTCCATATCAGGTTACTCAAATGAGTCGTCCAGACTTGATTCTCTTTCTGATGAAAT
ACCTGATGGCTCTCATAGTTGGCATTCCCTCTGTATTTTGGGTTGGAAGCAAAAAGACATGCTTT
GAATGGGCCAGTTTTTTTCATGGTTCGTAGGAAAAAAGAGATAGTGAATGAGAGCCGACAGGTA
CTCCAGGAACCTGATTTTGTCTCAGTCTCTCCTGAGGGATCCAAATACTCCTATCATAAGAAAGT
CAAGGGGAACCTTCCACTCAAGGAACATCCACCCATGCTTCTTCAACTCAGCTGGCTATGGTGGA
TGATCAAAGAAGCAAAGCAGGAAGCATCCACAGCAAAGTGAGCAGCTACCACGGCAGCCTCC
ACAGATCACGTGATGGCAGGTACACGCCCTGCAGTTACAGAGGAATGGAGGAGAGACTACCTC
ATGGCAGCATGTACGACTAACAGATCACTCCAGGCATAGTAGTTCTCATCGGCTCAATGAACA
GTCACGACATAGCAGCATCAGAGATCTCAGTAATAATCCCATGACTCATATCACACATGGCACC
AGCATGAATCGGGTTATTGAAGAAGATGGAACCAAGTGCCTTAATTTGTCTTGTCTAAGGTGGAAA
TCTGTGCTGTTTTAAAAAGCAGATTTTATCTTTGCCTTTTGCATGACTGATAGCTGTACTACA
GTTAACATGCTTTCAGTCAAGTACAGATTGTGTCCACTGGAAAGGTAAATGATTGCTTTTTTATA
TTGCATCAAACCTTGAACATCAAGGCATCCAAAACACTAAGAATTCTATCATCAGAAAAATAAT
TCGTCTTTCTAGGTTATGAAGAGATAATTATTTGTCTGGTAAGCATTTTTTATAAACCCTCATT
TTATATTTAGAAAAATCCTAAATGTGTGGTGAAGTCTTTGTAGTGAAGTTTCTATATACTATAAAC
TAGTTGTGAGATAACATTCTGGTAGCTCAGTTAATAAAACAATTTTCCAGATTAAAGAAATTTTC
TATGCAAGGTTTACTTCTCAGATGAACAGTAGGACTTTGTAGTTTTATTTCCACTAAGTGAAAA
AAGAACTGTGTTTTTAACTGTAGGAGAATTTAATAAATCAGCAAGGGTATTTTAGCTAATAGA
ATAAAAGTGCAACAGAGAATTTGATTAGTCTATGAAAGGTTCTCTTAAATTTCTATCGAAATA
ATCTTCATGCAGAGATATTCAGGGTTTGGATTAGCAGTGGAATAAAGAGATGGGCATTGTTTCC
CCTATAATTGTGCTGTTTTTATACTTTTGTAAATATTACTTTTTCTGGCTGTGTTTTTATACTT
ATCCATATGCATGATGGAAAAATTTTAATTTGTAGCCATCTTTTCCCATGTAATAGTATTGATTC
ATAGAGAACTTAATGTTCAAAATTTGCTTTGTGGAGGCATGTAATAAGATAAACATCATACATT
ATAAGGTAACCACAATTACAAAATGGCAAAACA

Figure 33

GCTGCGCAGCGCTGGCTGCTGGCTGGCCTCGCGGAGACGCCGAACGGACGCGGCCGGCGCCGG
CTTGTGGGCTCGCCGCTGCAGCCATGACCCTCGCAGCCTGTCCCTCGGCCTCGGCCCGGGACG
TCTAAAATCCCACACAGTCGCGCGCAGCTGCTGGAGAGCCGGCCGCTGCCCCCTCGTCGCCGCA

TCACACTCCCGTCCCGGGAGCTGGGAGCAGCGCGGGCAGCCGGCGCCCCGTGCAAACCTGGGG
GTGTCTGCCAGAGCAGCCCCAGCCGCTGCCGCTGCTACCCCCGATGCTGGCCATGGCCTGGCGG
GGCGCAGGGCCGAGCGTCCCGGGGGCGCCCGGGGGCGTCCGGTCTCAGTCTGGGGTTGCTCCTG
CAGTTGCTGCTGCTCCTGGGGCCGGCGCGGGGCTTCGGGGACGAGGAAGAGCGGGCGCTGCGAC
CCCATCCGCATCTCCATGTGCCAGAACCTCGGCTACAACGTGACCAAGATGCCAACCTGGTTG
GGCAGGAGCTGCAGACGGACGCCGAGCTGCAGCTGACAACTTTCACACCGCTCATCCAGTACG
GCTGCTCCAGCCAGCTGCAGTTCTTCTTTTGTCTGTTTATGTGCCAATGTGCACAGAGAAGATC
AACATCCCCATTGGCCCATGCGGGCGGCATGTGTCTTTCAGTCAAGAGACGCTGTGAACCCGTCC
TGAAGGAATTTGGATTTGCCCTGGCCAGAGAGTCTGAACTGCAGCAAATTTCCACCACAGAACG
ACCACAACCACATGTGCATGGAAGGGCCAGGTGATGAAGAGGTGCCCTTACCTCACAAAACCC
CCATCCAGCCTGGGGAAGAGTGTCACTCTGTGGGAACCAATTCTGATCAGTACATCTGGGTGAA
AAGGAGCCTGAACTGTGTGCTCAAGTGTGGCTATGATGCTGGCTTATACAGCCGCTCAGCCAAG
GAGTTCACTGATATCTGGATGGCTGTGTGGGCCAGCCTGTGTTTCACTCTCCACTGCCTTCACAGT
ACTGACCTTCTGATCGATTCTTCTAGGTTTTCTACCCTGAGCGCCCCATCATATTTCTCAGTA
TGTGCTATAATATTTATAGCATTGCTTATATTGTCAGGCTGACTGTAGGCCGGGAAAGGATATC
CTGTGATTTTGAAGAGGCAGCAGAACTGTTCTCATCCAAGAAGGACTTAAGAACACAGGATG
TGCAATAATTTCTTGCTGATGTACTTTTTTGAATGGCCAGCTCCATTTGGTGGGTATTCTGA
CACTCACTTGGTTTTTGGCAGCAGGACTCAAATGGGGTTCATGAAGCCATTGAAATGCACAGCTC
TTATTTCCACATTGCAGCCTGGGCCATCCCCGAGTGAAAACCATTTGTCATCTTGATTATGAGA
CTGGTGGATGCAGATGAACTGACTGGCTTGTGCTATGTTGGAAACCAAAATCTCGATGCCCTCA
CCGGGTTCTGGTGGCTCCCCTCTTACTTATTTGGTTCATTGGAACCTTTGTTTCATTGCTGCAGGT
TTGGTGGCCTTGTTCAAAATTCGGTCAAATCTTCAAAGGATGGGACAAAGACAGACAAGTTA
GAAAGACTGATGGTCAAGATTGGGGTGTCTCAGTACTGTACACAGTTTCTGCAACGTGTGTGA
TTGCCTGTTATTTTATGAAATCTCCAAGTGGGCACTTTTTCGGTATTCTGCAGATGATTCCAAC
ATGGCTGTTGAAATGTTGAAAACTTTTATGTCTTTGTTGGTGGGCATCACTTCAGGCATGTGGAT
TTGGTCTGCCAAAAGTCTTCACACGTGGCAGAAAGTGTCCAACAGATTGGTGAATTTCTGGAAG
GTAAAGAGAGAGAAGAGAGGAAATGGTTGGGTGAAGCCTGGAAAAGGCAGTGAGACTGTGGT
ATAAGGCTAGTCAGCCTCCATGCTTCTTCATTTTGAAGGGGGGAATGCCAGCATTTTGGAGGA
AATTCTACTAAAAGTTTTATGCAGTGAATCTCAGTTTGAACAACTAGCAACAATTAAGTGACC
CCCGTCAACCCACTGCCTCCCACCCGACCCCGAGCATCAAAAAACCAATGATTTTGTGTCAGAC
TTTGAATGATCCAAAATGGAAAAGCCAGTTAGAGGCTTTCAAAGCTGTGAAAAATCAAAACG
TTGATCACTTTAGCAGGTTGCAGCTTGGAGCGTGGAGGTCTGCCTAGATTCCAGGAAGTCCAG
GGCGATACTGTTTTCCCTGCAGGGTGGGATTTGAGCTGTGAGTTGGTAACAGCGGAGAGAAA
TATTAACTTTTTAAACCCTTTACCATTTTAAATACTAACTGGGTCTTTCAGATAGCAAAGCAATC
TATAAACTGGAAACGCTGGGTTCAGAAAAGTGTACAAAGAGTTTTATAGTTTGGCTGATGTA
ACATAAACATCTTCTGTGGTGGCTGTCTGTTTGAAGTCTTGTGGACTGCACTCCCAAGAA
GTGGTGTAGATACTTTTCAAGTGCCTTTGTCTATAAAACAGTTATTTGAACAAACAAAAGTACTGT
ACTCACACACATAAGGTATCCAGTGGATTTTCTTCTCTGTCTTCTCTTAAATTTCAACATCT
CTCTTCTTGGCTGCTGCTGTTTTCTTCATTTTATGTTAATGACTCAAAAAAGGTATTTTATAGAA
TTTTTGTACTGCAGCATGCTTAAAGAGGGGAAAAGGAAGGGTGATTCACTTTCTGACAATCACT
TAATTCAGAGGAAAATGAGATTTACTAAGTTGACTTACCTGACGGACCCAGAGACCTATTGCA
TTGAGCAGTGGGGACTTAATATATTTTACTTGTGTGATTGCATCTATGCAGACGCCAGTCTGGA
AGAGCTGAAATGTTAAGTTTCTTGGCAACTTTGCATTACACAGATTAGCTGTGTAATTTTTGTG
TGTCAATTACAATTAAGTAAAGCACATTGTTGGACCATGACATAGTATACTCAACTGACTTTAAAC
TATGGTCAACTTCAACTTGCATTCTCAGAATGATAGTGCCTTTAAATTTTTTATTTTTTAAAG
CATAAGAATGTTATCAGAATCTGGTCTACTTAGGACAATGGAGACTTTTTTCAAGTTTATAAAGG
GAACTGAGGACAGCTAATCCAACACTTGGTGTGTAATTGTTTCTAGTAATTGGCAAAGGCT
CCTTGTAAGATTTCACTGGAGGCAGTGTGGCCTGGAGTATTTATATGGTGCTTAATGAATCTCC
AGAATGCCAGCCAGAAGCCTGATTGGTTAGTAGGGAATAAAGTGTAGACCATATGAAATGAAC
TGCAAACCTAATAGCCCAGGTCTTAATTGCCCTTAGCAGAGGTATCCAAAGCTTTTAAATTT
ATGCATACGTTCTTCAAGGGGGTACCCCGAGCAGCCTCTCGAAAATTGCACTTCTCTTAAAC
CTGTAACCTGGCCTTTCTCTTACCTTGCCTTAGGCCTTCTAATCATGAGATCTTGGGGACAATTG
ACTATGTCACAGGTTGCTCTCCTTGTAACTCATACCTGTCTGCTTCAGCAACTGCTTTGCAATGA
CATTTATTTATTAATTATGCCTTAAAAAATAGGAAGGGAAGCTTTTTTTTTTTTTTTTTTTT
TTCAATCACACTTTGTGGAAAAACATTTCCAGGGACTCAAAATTCAAAAAGGTGGTCAAATTC
TGGAAGTAAGCATTTCTCTTTTTTAAAAATTTGGTTTGAGCCTTATGCCCATAGTTTGACATTT

CCCTTTCTTCTTTCCCTTTTGTGTTTTGTGTGGTTCCTTGAGCTCTCTGACATCAAGATGCATGTAAA
GTCGATTGTATGTTTTGAAGGCAAAGTCTTGGCTTTTGAGACTGAAGTTAAGTGGGCACAGGTG
GCCCCTGCTGCTGTGCCAGTCTGAGTACCTTGGCTAGACTCTAGGTCAGGCTCCAGGAGCATG
AGAATTGATCCCCAGAAGAACCATTTTAACTCCATCTGATACTCCATTGCCTATGAAATGTAAA
ATGTGAACTCCCTGTGCTGCTTGTAGACAGTTCCCATAACTGTCCACGGCCCTGGAGCACGCAC
CCAGGGGCAGAGCCTGCCCTTACTCACGCTCTGCTCTGGTGTCTTGGGAGTTGTGCAGGGACTC
TGGCCCAGGCAGGGGAAGGAAGACCAGGCGGTAGGGGACTGGTCTTGCTGTTAGAGTATAGAG
GTTTGTAAATGCAGTTTTCTTCATAATGTGTCACTGATTGTGTGACCAAGGCAGCATCTAGCAGA
AAGCCAGGCATGGAGTAGGTGATCGATACTTGTCAATGACTAAATAATAACAATAAAAGAGCA
CTTGGGTGAATCTGGGCACCTGATTTCTGAGTTTGTAGTTCTGGAGCTAGTGTGTTGACAATGCT
TTGGGTTTTGACATGCCCTTTCCACAAATCTCTTGCCTTTTCAGGGCAAAGTGTATTTGATCAGA
AGTGGCCATTTGGATTAGTAGCCTTAGCAATGCTACAGGGTTATAGGCCCTCTCCCTTTTCACAT
TCCAGACAATGGAGAGTGTTTATGGTTTCAGGAAAAGAACTTTGTGGCTGAGGGGTCAGTTACC
AGTGACCTTCAATCAACTCCATCACTTCTTAAATCGGTATTTGTAAAAAATCAGTTATTTTAT
TTATTGAGTGCCGACTGTAGTAAAGCCCTGAAATAGATAATCTCTGTTCTTCTAACTGATCTAG
GATGGGGACGCACCCAGGTCTGCTGAACTTTACTGTTCTCTGGGAAAGGAGCAGGGACCTCTG
GAATTTCCCATCTGTTTCACTGTCTCCATCTCCATAAACTCTTCTCTGTGTGAGCCACCACACCCAG
CCTGGGTCTCTCTACTTTTAAACACATCTCTCATACCTTTTCCAGGACTTCTTCCAGTCAGTTAC
AGGTGGTTTTTAACAGAAAGCATCAGCTCTGCTTCGTGACAGTCTCTGGAGAAATCCCTTAGGAA
GACTATGAGAGTAGGCCACAAGGACATGGGCCACACATCTGCTTTGGCTTTGCCGCAATTCA
GGCTTTGGGTATTCCATGTGACTTGTATAGGTATATTTGAGGACAGCATCTTGCTAGAGAAAA
GGTGAGGGTTGTTTTTCTTCTCTGAAACCTACAGTAAATGGGTATGATTGTAGCTTCTCAGAA
ATCCCTTGCCCTCCAGAGATTAAACATGGTGCAATGGCACCTCTGTCCAACCTCCTTTCTGGTA
GATTCCTTTCTCTGCTTCATATAGGCCAAACCTCAGGGCAAGGGAACATGGGGGTAGAGTGGT
GCTGGCCAGAACCATCTGCTTGAGCTACTTGGTTGATTTCATATCCTCTTTCTTTATGGAGACCC
ATTTCTGATCTCTGAGACTGTTGCTGAACTGGCAACTTACTTGGGCCTGAACTGGAGAAGGG
GTGACATTTTTTTAATTTAGAGATGCTTTCTGATTTTCTCTCCAGGTCACTGTCTCACCTGCA
CTCTCCAAACTCAGGTTCCGGGAAGCTTGTGTGTCTAGATACTGAATTGAGATTCTGTTTCAGCA
CCTTTTAGCTCTATACTCTCTGGCTCCCTCATCCTCATGGTCACTGAATTAATGCTTATTGTAT
TGAGAACCAAGATGGGACCTGAGGACACAAAGATGAGCTCAACAGTCTCAGCCCTAGAGGAAT
AGACTCAGGGATTTACCAGGTGCGTGCAGTATTTGATTTCTGGTGAGGTGACCACAGCTGCAG
TTAGGAAGGGAGCCATTGAGCACAGACTTGGAAAGGAACCTTTTTTTGTTGTTTGTGTTGT
TTGTTTGTGTTGTTGTTGAGACAGGGTCTTGCTCTGCTACCCAGGCTGGGGCGCAATGGCACGA
TCTTGGCTCACTGCAACCTCTGCCTCCTGGGTTCAAGTGATTCTCCTGCCACAGCCTCCTGAGGA
GCTGGGACTACAGGTGCGTGCTACCACGCCCAGCTACTTCTGTATTTTTAGTAGAGACGGGGTT
TCACTGTGTTGGCCAGGCTGGTCTCGAACCCTGACTCATGATCTGCCCGCCTCAGCCTCCCAA
AGTGCTGGGATTACAAGTGTGAGCCACCACACCTGGCCTGGAAGGAACCTCTTAAATCAGTTT
ACGTCTTGATTTTTGTTCTGTGATGGAGGACACTGGAGAGAGTTGCTATTCCAGTCAATCATGTC
GAGTCACTGGACTCTGAAAATCCTATTGGTTCCTTTATTTTATTTGAGTTTAGAGTTCCCTTCTG
GGTTTGATATTATGTCTGGCAAATGACCTGGGTTATCACTTTTCTCCAGGGTTAGATCATAGATC
TTGGAACCTCCTTAGAGAGCATTTTGCTCCTACCAAGGATCAGATACTGGAGCCCCACATAATA
GATTTCAATTCACCTCTAGCCTACATAGAGCTTTCTGTTGCTGTCTCTTGCCATGCACTTGTGCGG
TGATTACACACTTGACAGTACCAGGAGACAAATGACTTACAGATCCCCCGACATGCCTCTTCCC
CTTGGCAAGCTCAGTTGCCCTGATAGTAGCATGTTTCTGTTTCTGATGTACCTTTTTTCTCTTCT
CTTTGCATCAGCCAATTTCCAGAAATTTCCCCAGGCAATTTGTAGAGGACCTTTTTGGGGTCCAT
ATGAGCCATGTCCTCAAAGCTTTTAAACCTCCTTGCTCTCCTACAATATTAGTACATGACCACT
GTCATCCTAGAAGGCTTCTGAAAAGAGGGGCAAGAGCCACTCTGCGCCACAAAGGTTGGATCC
ATCTTCTCTCCGAGGTTGTGAAAAGTTTTCAAATTTGTAATAAGGCTGGGGCCCTGACTTGGCTG
TGGGCTTTGGGAGGGGTAAGCTGCTTTCTAGATCTCTCCAGTGAGGCATGGAGGTGTTTCTGA
ATTTTGTCTACCTCACAGGGATGTTGTGAGGCTTGAAGGTCAAAAAATGATGGCCCCCTGAG
CTCTTTGTAAGAAAGGTAGATGAAATATCGGATGTAATCTGAAAAAAGATAAAATGTGACTT
CCCCGTGCTCTGTGCAGCAGTCGGGCTGGATGCTCTGTGGCNTTTCTTGGGTCTCATGCCACCCC
ACAGCTCCAGGAACCTTGAAGCCAATCTGGGGACTTTTCAAGATGTTTGACAAAGAGTACCAGG
CAAACCTTCTGCTACACATGCCCTGAATGAATTGCTAAATTTCAAAGGAAATGGACCTGCTTT
TAAGGATGTACAAAAGTATGTCTGCATCGATGTCTGTACTGTAAATTTCTAATTTATCACTGTAC

29/41

AAAGAAAACCCCTTGCTATTTAATTTTGTATTAAAGGAAAATAAAGTTTTGTTTGTAAAAAA
AA

Figure 34

ACCCAGGGACGGAGGACCCAGGCTGGCTTGGGGACTGTCTGCTCTTCTCGGCGGGAGCCGTGG
AGAGTCCTTTCCCTGGAATCCGAGCCCTAACCGTCTCTCCCCAGCCCTATCCGGCGAGGAGCGG
AGCGCTGCCAGCGGAGGCAGCGCCTTCCCGAAGCAGTTTATCTTTGGACGGTTTTCTTTAAAGG
AAAAACGAACCAACAGGTTGCCAGCCCCGGCGCCACACACGAGACGCCGGAGGGAGAAGCCC
CGGCCCCGATTCTCTGCCTGTGTGCGTCCCTCGCGGGCTGCTGGAGGCGAGGGGAGGGAGGG
GGCGATGGCTCGGCCTGACCCATCCGCGCCGCCCTCGCTGTTGCTGCTGCTCCTGGCGCAGCTG
GTGGGCCGGGCGGCCGCGCGTCCAAGGCCCCGGTGTGCCAGGAAATCACGGTGCCCATGTGC
CGCGGCATCGGCTACAACCTGACGCACATGCCCAACCAGTTCAACCACGACACGCAGGACGAG
GCGGGCCTGGAGGTGCACCAAGTTCTGGCCGCTGGTGGAGATCCAATGCTCGCCGGACCTGCGCT
TCTTCTATGCACTATGTACACGCCCATCTGTCTGCCGACTACCACAAGCCGCTGCCGCCCTGC
CGCTCGGTGTGCGAGCGCGCCAAGGCGGGCTGCTCGCCGCTGATGCGCCAGTACGGCTTCGCCT
GGCCCGAGCGCATGAGCTGCGACCGCCTCCCGGTGCTGGGCCGCGACGCCGAGGTCCTCTGCA
TGGATTACAACCGCAGCGAGGCCACCACGGCGCCCCCAGGCCTTTCCAGCCAAGCCCACCCT
TCCAGGCCCGCCAGGGGCGCGGCCCTCGGGGGCGAATGCCCGCTGGGGGCCGTTTCGTGTG
CAAGTGTGCGAGCCCTTCGTGCCATTCTGAAGGAGTCACACCCGCTCTACAACAAGGTGCGG
ACGGGCCAGGTGCCCAACTGCGCGGTACCCTGCTACCAGCCGTCCTTCAGTGCCGACGAGCGC
ACGTTGCGCACCTTCTGGATAGGCCTGTGGTGGTGTGCTGTGCTTCATCTCCACGTCCACCACAGT
GGCCACCTTCTCATCGACATGGACACGTTCCGCTATCCTGAGCGCCCCATCATCTTCCTGTGAG
CCTGCTACCTGTGCGTGTGCTGGGCTTCTGTGCGTCTGGTCTGTTGGCCATGCCAGCGTGGC
CTGCAGCCGCGAGCACAACCACATCCACTACGAGACCACGGGCCCTGCACTGTGCACCATCGT
CTTCTCTGGTCTACTTCTTCGGCATGGCCAGCTCCATCTGGTGGGTTCATCTGCTGCTCACCT
GGTTCCTGGCCCGCGCATGAAGTGGGGCAACGAGGCCATCGCGGGCTACGGCCAGTACTTCC
ACCTGGCTGCGTGGCTCATCCCCAGCGTCAAGTCCATCACGGCACTGGCGCTGAGCTCCGTGGA
CGGGGACCCAGTGGCCGGCATCTGCTACGTGGGCAACCAGAACCTGAACCTGCTGCGGCGCTT
CGTGCTGGGCCCCGCTGGTGTCTACCTGCTGGTGGGCACGCTCTTCTGCTGGCGGGCTTCGTGT
CGCTCTTCCGCATCCGCAGCGTCATCAAGCAGGGCGGCACCAAGACGGACAAGCTGGAGAAGC
TCATGATCCGCATCGGCATCTTACGCTGCTCTACACGGTCCCCGCCAGCATTGTGGTGGCCTG
CTACCTGTACGAGCAGCACTACCGCGAGAGCTGGGAGGCGCGCTCACCTGCGCCTGCCCGGG
CCACGACACCGGCCAGCCGCGCGCCAAGCCGAGTACTGGGTGCTCATGCTCAAGTACTTTCATG
TGCCTGTGTGGTGGGCATCACGTGCGGCGTCTGGATCTGGTTCGGGCAAGACGGTGGAGTCGTGG
CGGCGTTTACAGCGCGCTGCTGCTGCCGCCCGCGGCGCGCCACAAGAGCGGGGGCGCCATG
GCCGACGGGACTACCCGAGGCGAGCGCCGCGCTCACAGGACGAGCCGGGCCGCGGGCCCC
GCCGCCACCTACCACAAGCAGGTGTCCCTGTGCGACGTGTAGGAGGCTGCCGCCGAGGGACTC
GGCCGAGAGCTGAGGGGAGGGGGCGTTTTGTTTGGTAGTTTTGCCAAGGTCACTTCCGTTTA
CCTTCATGGTGTGTTGCCCCCTCCCGCGGCGACTTGGAGAGAGGGAAGAGGGGCGTTTTGAG
GAAGAACCTGTCCAGGTCTTCTCCAAGGGGCCAGCTCACGTGTATTCTATTTTGCCTTTCTTA
CCTGCCCTTTTATGGGAACCCTCTTTTAAATTTATATGTAT

Figure 35

GCAGCTCCAGTCCCGGACGCAACCCCGGAGCCGTCTCAGGTCCCTGGGGGGAACGGTGGGTTA
GACGGGGACGGGAAGGGACAGCGGCCTTCGACCGCCCCCGAGTAATTGACCCAGGACTCATT
TTCAGGAAAGCCTGAAAATGAGTAAAATAGTGAAATGAGGAATTTGAACATTTTATCTTTGGAT
GGGGATCTTCTGAGGATGCAAAGAGTGATTCATCCAAGCCATGTGGTAAAATCAGGAATTTGA
AGAAAATGGAGATGTTTACATTTTGTGACGTGTATTTTCTACCCCTCCTAAGAGGGACAGT
CTCTTCACCTGTGAACCAATTACTGTTCCAGATGTATGAAAATGGCCTACAACATGACGTTTTT
CCCTAATCTGATGGGTCAATTATGACCAGAGTATTGCCGCGGTGGAAAATGGAGCATTTTCTTCCT
CTCGCAAATCTGGAATGTTACCAAACATTGAAACTTTCTCTGCAAAGCATTTGTACCAACCT
GCATAGAACAAATTCATGTGTTCCACCTTGTCGTAAACTTTGTGAGAAAGTATATTCTGATTG

CAAAAAATTAATTGACACTTTTGGGATCCGATGGCCTGAGGAGCTTGAATGTGACAGATTACAA
TACTGTGATGAGACTGTTCTGTAACTTTTGATCCACACACAGAATTTCTTGGTCTCAGAAGA
AAACAGAACAGTCCAAAGAGACATTGGATTTTGGTGTCCAAGGCATCTTAAGACTTCTGGGG
GACAAGGATATAAGTTTCTGGAATTGACCAGTGTGCGCCTCCATGCCCCAACATGTATTTTAA
AAGTGATGAGCTAGAGTTTGCAAAAAGTTTTATTGGAACAGTTTCAATATTTTGTCTTTGTGCA
ACTCTGTTACATTCTTACTTTTTTAATTGATGTTAGAAAGATTGAGATACCCAGAGAGACCAAT
TATATATTACTCTGTCTGTTACAGCATTGTATCTTATGTACTTCATTGGATTTTGTCTGGGCGA
TAGCACAGCCTGCAATAAGGCAGATGAGAAGCTAGAACTTGGTGACACTGTTGTCCTAGGCTCT
CAAAATAAGGCTTGACACGTTTTGTTTCATGCTTTTGTATTTTTTCACAATGGCTGGCACTGTGTG
GTGGGTGATTCTTACCATTACTTGGTTCCTAGCTGCAGGAAGAAAATGGAGTTGTGAAGCCATC
GAGCAAAAAGCAGTGTGGTTTCATGCTGTTGCATGGGGAACACCAGGTTTCCTGACTGTTATGC
TTCTTGCTCTGAACAAAAGTTGAAGGAGACAACATTAGTGGAGTTTGTCTTGTGGCCTTCTCT
CCTGGATGCTTCTCGCTACTTTGTACTCTTGCCACTGTGCCTTTGTGTGTTTGTGGCTCTCTCT
TCTTTTAGCTGGCATTATTTCTTAAATCATGTTTCGACAAGTCATACAACATGATGGCCGGAACC
AAGAAAACTAAAGAAATTTATGATTTCGAATTGGAGTCTTCAGCGGCTTGTATCTTGTGCCATT
AGTGACACTTCTCGGATGTTACGTCTATGAGCAAGTGAACAGGATTACCTGGGAGATAACTTGG
GTCTCTGATCATTGTCTGTCAGTACCATATCCCATTGCTTATCAGGCAAAAAGCAAAAGCTCGAC
CAGAATTTGGCTTTATTTATGATAAAATACCTGATGACATTAATTGTTGGCATCTCTGCTGTCTTC
TGGGTTGGAAGCAAAAAGACATGCACAGAATGGGCTGGGTTTTTTAAACGAAATCGCAAGAGA
GATCCAATCAGTGAAAGTCAAGAGTACTACAGGAATCATGTGAGTTTTTCTTAAAGCACAATT
CTAAAGTTAAACACAAAAAGCAACTATAAACCAAGTTCACACAAGCTGAAGGTCATTTCGA
AATCCATGGGAACCAGCACAGGAGCTACAGCAAATCATGGCACTTCTGCAGTAGCAATTACTA
GCCATGATTACCTAGGACAAGAACTTTGACAGAAATCCAAACCTCACCAGAAACATCAATGA
GAGAGGTGAAAGCGGACGGAGCTAGCACCCCCAGGTTAAGAGAACAGGACTGTGGTGAACCT
GCCTCGCCAGCAGCATCCATCTCCAGACTCTCTGGGGAACAGGTCGACGGGAAGGGCCAGGCA
GGCAGTGTATCTGAAAGTGCAGGAGTGAAGGAAGGATTAGTCCAAAGAGTGATATTACTGAC
ACTGGCCTGGCACAGAGCAACAATTTGACAGTCCCCAGTTCCTCAGAACCAAGCAGCCTCAAA
GGTTCCACATCTCTGCTTGTTCACCCAGTTTCAGGAGTGAGAAAAGAGCAGGGAGGTGGTTGTC
ATTCAGATACTTGAAGAACATTTTCTCTCGTTACTCAGAAGCAAAATTTGTGTTACTGGAAGT
GACCTATGCACTGTTTTGTAAAGAACACTGTTACGTTCTTCTTTTGCACTTAAAGTTGCATTGCC
TACTGTTATACTGGAAAAATAGAGTTCAAGAATAATATGACTCATTTACACAAAGGTTAATG
ACAACAATATACCTGAAAACAGAAATGTGCAGGTTAATAATATTTTTTTAATAGTGTGGGAGGA
CAGAGTTAGAGGAATCTTCCTTTTCTATTTATGAAGATTCTACTCTTGGTAAGAGTATTTTAAAG
TGTAATATGCTATTTTACCTTTTATATATAAAATCAAGATATTTCTTTGCTGAAGTATTTAAATCT
TATCCTTGATCTTTTTATACATATTTGAAAATAAGCTTATATGTATTTGAACTTTTTTGAAATCC
TAAGAAAATTGTAATAAGTCTTCTTTTATATCTGTAATAAAAGATATACCAAAAAGTCTTATAA
TAGGAATTTAACTTTAAAAACCCACTTATTGATACCTTACCATCTAAAATGTGTGATTTTATAG
TCTCGTTTTAGGAATTTACAGATCTAAATTATGTAAGTGAATAAGGTGCTTACTCAAAGAGT
GTCCACTATTGATTGTATTATGCTGCTCACTGATCCTTCTGCATATTTAAAATAAAATGTCCTAA
AGGGTTAGTAGACAAAATGTTAGTCTTTTGTATATTAGGCCAAGTGCAATTGACTTCCCTTTTTT
AATGTTTCATGACCACCCATTGATTGTATTATAACCACTTACAGTTGCTTATATTTTTTGTTTAA
CTTTTGTCTTAAACATTTAGAATATTACATTTTGTATTATACAGTACCTTCTCAGACATTTTGT
AG

Figure 36

CTCTCCCAACCGCCTCGTCGCACTCCTCAGGCTGAGAGCACCGCTGCACTCGCGGCCGCGGATG
CGGGACCCCGGCGCGGCCGCTCCGCTTTCGTCCCTGGGCCTCTGTGCCCTGGTGTGGCGCTGC
TGGGCGCACTGTCCGCGGGCGCGGGGCGCAGCCGTACCACGGAGAGAAGGGCATCTCCGTGC
CGGACCACGGCTTCTGCCAGCCCATCTCCATCCCGCTGTGCACGGACATCGCTACAACCAGAC
CATCCTGCCCAACCTGCTGGGCCACACGAACCAAGAGGACGCGGGCCTCGAGGTGCACCAGTT
CTACCCGCTGGTGAAGGTGCAAGTGTCTCCCGAACTCCGCTTTTTCTTATGCTCCATGTATGCGC
CCGTGTGCACCGTGCTCGATCAGGCCATCCCGCCGTGTCGTTCTCTGTGCGAGCGCGCCGCCA

GGGCTGCGAGGCGCTCATGAACAAGTTCGGCTTCCAGTGGCCCGAGCGGCTGCGCTGCGAGAA
CTTCCCGGTGCACGGTGC GGCGAGATCTGCGTGGGCCAGAACACGTCGGACGGCTCCGGGGG
CCCAGGCGGGCGGCCCCACTGCCTACCTACCGCGCCCTACCTGCCGGACCTGCCCTTACCGCG
CTGCCCCCGGGGGCCTCAGATGGCAGGGGGCGTCCCGCCTTCCCCTTCTCATGCCCCCGTCAGC
TCAAGGTGCCCCCGTACCTGGGCTACCGCTTCCCTGGGTGAGCGCGATTGTGGCGCCCCGTGCGA
ACCGGGCCGTGCCAACGGCCTGATGTACTTTAAGGAGGAGGAGAGGCGCTTCGCCCGCCTCTG
GGTGGGCGTGTGGTCCGTGCTGTGCTGCGCCTCGACGCTCTTACCGTTCTCACCTACCTGGTGG
ACATGCGGCGCTTCAGCTACCCAGAGCGGCCCATCATCTTCTGTCGGGCTGCTACTTCATGGT
GGCCGTGGCGCACGTGGCCGGCTTCCCTCTAGAGGACCGCGCCGTGTGCGTGGAGCGCTTCTCG
GACGATGGCTACCGCACGGTGGCGCAGGGCACCAAGAAGGAGGGCTGCACCATCCTCTTCATG
GTGCTCTACTTCTTCGGCATGGCCAGCTCCATCTGGTGGGTCACTTCTGTCTCACTTGGTTCCT
GGCGGCCGGCATGAAGTGGGGCCACGAGGCCATCGAGGCCAACTCGCAGTACTTCCACCTGGC
CGCGTGGGCCGTGCCCCCGTCAAGACCATCACTATCCTGGCCATGGCCAGGTAGACGGGA
CCTGCTGAGCGGGGTGTGCTACGTTGGCCTCTCCAGTGTGGACGCGCTGCGGGGCTTCGTGCTG
GCGCCTCTGTTCTGCTACCTCTTCATAGGCACGTCCTTCTTGCTGGCCGGCTTCGTGTCCCTCTC
CGCATCGGCGTCTTCAGCGTGTCTACACAGTGCCCGCCACCATCGTCTGGCCTGCTACTTCTA
CGAGCAGGCTTCCGCGAGCACTGGGAGCGCACCTGGCTCCTGCAGACGTGCAAGAGCTATGC
CGTGCCCTGCCCGCCCGCCACTTCCCGCCCATGAGCCCCGACTTCACCGTCTTCATGATCAAG
TACCTGATGACCATGATCGTCGGCATCACCCTGGCTTCTGGATCTGGTTCGGGCAAGACCCTGC
AGTCGTGGCGCCGCTTCTACCACAGACTTAGCCACAGCAGCAAGGGGGAGACTGCGGTATGAG
CCCCGGCCCCCTCCCCACCTTTCCACCCCCAGCCCTCTTGCAAGAGGAGAGGCACGGTAGGGAAA
AGAACTGCTGGGTGGGGGCCTGTTTCTGTAACCTTCTCCCCCTCTACTGAGAAGTGACCTGGAA
GTGAGAAGTTCTTTGCAGATTTGGGGCGAGGGGTGATTTGGAAAAGAAGACCTGGGTGGAAAG
CGGTTTGGATGAAAAGATTTCAAGCAAAGACTTGCAGGAAGATGATGATAACGGCGATGTGAA
TCGTCAAAGGTACGGGCCAGCTTGTGCCTAATAGAAGGTTGAGACCAGCAGAGACTGCTGTGA
GTTTCTCCCGGCTCCGAGGCTGAACGGGGACTGTGAGCGATCCCCCTGCTGCAGGGCGAGTGGC
CTGTCCAGACCCCTGTGAGGCCCGGGAAAGGTACAGCCCTGTCTGCGGTGGCTGCTTTGTTGG
AAAGAGGGAGGGCCTCCTGCGGTGTGCTTGTCAAGCAGTGGTCAAACCATAATCTCTTTTCACT
GGGGCCAAACTGGAGCCCAGATGGGTTAATTTCCAGGGTCAGACATTACGGTCTCTCCTCCCCCT
GCCCCCTCCCGCCTGTTTTTCTCCCGTACTGCTTTCAGGTCTTGTAATAAGCATTGGAAGT
CTTGGGAGGCCTGCCTGCTAGAATCCTAATGTGAGGATGCAAAAGAAATGATGATAACATTTTG
AGATAAGGCCAAGGAGACGTGGAGTAGGTATTTTGTACTTTTTCATTTTCTGGGGAAGGCAG
GAGGCAGAAAGACGGGTGTTTTATTTGGTCTAATACCCTGAAAAGAAGTGATGACTTGTGCTT
TTCAAAACAGGAATGCATTTTTCCCTTGTCTTTGTGTAAGAGACAAAAGAGGAAACAAAAGT
TGAGGTTTCCCGTTGGTTGTTAATTTGGTTGAGATAAACATTCCTTTTTAAGGAAAAGTGAAGA
GCAGTGTGCTGTACACACCGTTAAGCCAGAGGTTCTGACTTCGCTAAAGGAAATGTAAGAGG
TTTTGTTGTCTGTTTTAAATAAATTTAATTCGGAACACATGATCCAACAGACTATGTTAAAATAT
TCAGGGAAATCTCTCCCTTCATTTACTTTTTCTTGCTATAAGCCTATATTTAGGTTTCTTTTCTAT
TTTTTCTCCCATTTGGATCCTTTGAGGTAAAAAACATAATGTCTTCAGCCTCATAATAAAGGA
AAGTTAATTAATAAAAAAAGCAAAGAGCCATTTTGTCTGTTTTCTTGTTCCATCAATCTGT
TTATTAACATCATCCATATGCTGACCCTGTCTCTGTGTGGTTGGGTGGGAGGCGATCAGCAG
ATACCATAGTGAACGAAGAGGAAGGTTTGAACCATGGGCCCCATCTTTAAAGAAAGTCATTAA
AAGAAGGTAACTTCAAAGTGATTCTGGAGTTCTTTGAAATGTGCTGGAAGACTTAAATTTATT
AATCTTAAATCATGTACTTTTTTCTGTAATAGAACTCGGATTCTTTTGCATGATGGGGTAAAGC
TTAGCAGAGAATCATGGGAGCTAACCTTTATCCACCTTTGACACTACCCTCCAATCTTGCAAC
ACTATCCTGTTTCTCAGAACAGTTTTTAAATGCCAATCATAGAGGGTACTGTAAAGTGTACAAG
TTACTTTATATATGTAATGTTCACTTGAGTGGAAGTGCCTTTTACATTAAAGTTAAATCGATCT
TGTGTTTCTTCAACCTTCAAACTATCTCATCTGTGAGATTTTTTAAACTCCAACACAGGTTTTG
GCATCTTTTGTGCTGTATCTTTAAGTGCATGTGAAATTTGTAAAATAGAGATAAGTACAGTAT
GTATATTTTGTAAATCTCCCATTTTTGTAAAGAAATATATATTGTATTTATACATTTTACTTTGG
ATTTTTGTTTTGTTGGCTTTAAAGGTCTACCCCACTTTATCATGTACAGATCACAAATAAATT
TTTTTAAATAC

Figure 37

32/41

ACAGCATGGAGTGGGGTTACCTGTTGGAAGTGACCTCGCTGCTGGCCGCCTTGGCGCTGCTGCA
GCGCTCTAGCGGCGCTGCGGCCGCTCGGCCAAGGAGCTGGCATGCCAAGAGATCACCGTGCC
GCTGTGTAAGGGCATCGGCTACAACTACACCTACATGCCCAATCAGTTCAACCACGACACGCA
AGACGAGGCGGGCCTGGAGGTGCACCAAGTTCTGGCCGCTGGTGGAGATCCAGTGCTCGCCCGA
TCTCAAGTTCTTCTGTGCAGCATGTACACGCCCATCTGCCTAGAGGACTACAAGAAGCCGCTG
CCGCCCTGCCGCTCGGTGTGCGAGCGCGCCAAGGCCGGCTGCGCGCCGCTCATGCGCCAGTAC
GGCTTCGCCTGGCCCGACCGCATGCGCTGCGACCGGCTGCCCGAGCAAGGCAACCCTGACACG
CTGTGCATGGACTACAACCGCACCGACCTAACCACCGCCGCGCCAGCCCGCCGCGCCGCTGC
CGCCGCGCGCCGCGCGGAGCAGCGCCTTCGGGCAGCGGCCACGGCCGCGCCGCGGGGGCCA
GGCCCCCGCACCGCGGAGGCGGCAGGGGCGGTGGCGGCGGGGACGCGGCGGCGCCCCAGCT
CGCGGCGGCGGCGGTGGCGGGAAGGCGCGGCCCTGGCGGCGGCGGGCTCCCTGCGAGCCC
GGGTGCCAGTGCCGCGCGCCTATGGTGAGCGTGTCCAGCGAGCGCCACCCGCTCTACAACCG
GTCAAGACAGGCCAGATCGCTAACTGCGCGTGTCCCTGCCACAACCCCTTTTCAGCCAGGACG
AGCGCGCCTTACCGTCTTCTGGATCGGCCTGTGGTGGTGTCTGCTTCTGCTTCCACCTTCGCC
ACCGTCTCCACCTTCTTATCGACATGGAGCGCTTCAAGTACCCGGAGCGGCCATTATCTTCTT
CTCGGCTGCTACCTCTTCTGTGTCGGTGGGCTACCTAGTGCGCCTGGTGGCGGGCCACGAGAAG
GTGGCGTGACGCGGTGGCGCGCCGGGCGCGGGGGCGCTGGGGGCGCGGGCGGCGCGGCGGC
GGGCGCGGGCGCGGCGGGGCGCGGGCGCGGGCGGCCGCGGGCGGCGGCGAGTACGAGGAGC
TGGGCGCGGTGGAGCAGCACGTGCGCTACGAGACCACCGGCCCGCGCTGTGCACCGTGGTCT
TCTTGCTGGTCTACTTCTTCGGCATGGCCAGCTCCATCTGGTGGGTGATCTTGTGCTCACATGG
TTCCTGGCGGCCGATGAAGTGGGGCAACGAAGCCATCGCCGGCTACTCGCAGTACTTCCACC
TGGCCGCGTGGCTTGTGCCAGCGTCAAGTCCATCGCGGTGCTGGCGCTCAGCTCGGTGGACGG
CGACCCGGTGGCGGGCATCTGCTACGTGGGCAACCAGAGCCTGGACAACCTGCGCGGCTTCGT
GCTGGCGCCGCTGGTCATCTACCTCTTCATCGGCACCATGTTCTGCTGGCCGGCTTCGTGTCCC
TGTTCCGCATCCGCTCGGTTCATCAAGCAACAGGACGGCCCCACCAAGACGCACAAGCTGGAGA
AGCTGATGATCCGCCTGGGCCTGTTACCCGTGCTCTACACCGTGCCCGCCGCGGTGGTGGTGC
CTGCCTCTTCTACGAGCAGCACAACCGCCCGCGCTGGGAGGCCACGCACAACCTGCCCGTGCCTG
CGGGACCTGCAGCCCGACCAAGCACGCAGGCCCGACTACGCCGTCTTCATGCTCAAGTACTTCA
TGTGCCTAGTGGTGGGCATCACCTCGGGCGTGTGGGTCTGGTCCGGCAAGACGCTGGAGTCTG
GCGTCCCTGTGCACCCGCTGCTGCTGGGCCAGCAAGGGCGCCGCGGTGGGCGGGGGCGCGGG
CGCCACGGCCGCGGGGGGTGGCGGCGGGCCGGGGGGCGGCGGCGGCGGGGGACCCGCGGGCG
GCGGGGGCGGGGCGGCGGCGGGGGCTCCCTCTACAGCGACGTCAGCACTGGCCTGACGTGGC
GGTCGGGCACGGCGAGCTCCGTGTCTTATCAAAGCAGATGCCATTGTCCAGGTCTGAGCGGA
GGGAGGGGGCGCCAGGAGGGGTGGGAGGGGGCGAGGAGACCCAAGTGCAGCGAAGGG
ACACTTGTATGGGTGAGGTTCCACCCCTTACAGTGTGATTGCTATTAGCATGATAATGAAC
TCTAATGGTATCCATTAGCTGGGACTTAAATGACTCACTTAGAACAAAGTACCTGGCATTGAA
GCCTCCCAGACCCAGCCCCTTTTCTCCATTGATGTGCGGGGAGCTCCTCCCGCCACGCGTTAAT
TTCTGTTGGCTGAGGAGGGTGGACTCTGCGGCGTTTCCAGAACCCGAGATTTGGAGCCCTCCCT
GGCTGCACTTGGCTGGGTTTGCAGTCAGATACACAGATTTACCTGGGAGAACCTCTTTTTCTCC
CTCGACTCTTCTACGTAAACTCCCACCCCTGACTTACCCTGGAGGAGGGGTGACCGCCACCTG
ATGGGATTGCACGGTTTGGGTATTCTTAATGACCAGGCAAAATGCCTTAAGTAAACAAACAAGA
AATGTCTTAATTATACACCCACGTAAATACGGGTTTCTTACATTAGAGGATGTATTTATATAAT
TATTTGTTAAATTGTAAAAAAGTTAGAGGCTTACCCCTGTAAGAACAGATATAAGTATTCTATTTTGTCA
ATAAAATGACTTTTGATAAATGATTAAACATTGCCCTCTCCCCGCGCTTCTGAGCTGTACAC
TTTAAAGTGCTTGCTAAGGACGCATGGGGAAAATGGACATTTTCTGGCTTGTATTCTGTACAC
TGACCTTAGGCATGGAGAAAATTACTTGTAAACTCTAGTTCTTAAGTTGTTAGCCAAGTAAAT
ATCATTGTTGAACTGAAATCAAAATTGAGTTTTTGCACCTTCCCCAAAGACGGTGTTTTTCATGG
GAGCTCTTTCTGATCCATGGATAACAACCTCTCACTTAGTGGATGTAAATGGAACCTCTGCAA
GGCAGTAATTCCTTAGGCCTTGTATTTATCCTGCATGGTATCACTAAAGGTTTCAAAACCCT
GAAAAAAA

Figure 38

33/41

CCGCCTTCGGCCCCGGGCTCCCGGGATGGCCGTGGCGCCTCTGCGGGGGGCGCTGCTGCTGTGG
CAGCTGCTGGCGGCGGGCGGCGCGGCACTGGAGATCGGCCGCTTCGACCCGGAGCGCGGGCGC
GGGGCTGCGCCGTGCCAGGCGGTGGAGATCCCATGTGCCGCGGCATCGGCTACAACCTGACC
CGCATGCCAACCTGCTGGGCCACACGTCGCAAGGGCGAGGCGGCTGCCGAGCTAGCGGAGTTC
GCGCCGCTGGTGCAGTACGGCTGCCACAGCCACCTGCGCTTCTTCCTGTGCTCGCTCTACGCGC
CCATGTGCACCGACCAGGTCTCGACGCCCATTCCCGCCTGCCGGCCCATGTGCGAGCAGGCGCG
CCTGCGCTGCGCGCCCATCATGGAGCAGTTCAACTTCGGCTGGCCGGA CTGCTCGACTGCGCC
CGGCTGCCACGCGCAACGACCCGCACGCGCTGTGCATGGAGGCGCCCGAGAACGCCACGGCC
GGCCCCGCGGAGCCCCACAAGGGCCTGGGCATGCTGCCCGTGGCGCCGCGGCCCGCGCGCCCT
CCCGGAGACCTGGGCCCCGGGCGCGGGCGGCAGTGGCACCTGCGAGAACCCCGAGAAGTTCCAG
TACGTGGAGAAGAGCCGCTCGTGCGCACCGCGCTCGGGGCCCGGCGTGCAGGTGTTCTGGTCC
CGGCGCGACAAGGACTTCGCGCTGGTCTGGATGGAGCCCCACCGCTTCCAGTACCCGAGCGCCCCATC
CCGCCTTCACTGTGCTCACCTTCTTGCTGGAGCCCCACCGCTTCCAGTACCCGAGCGCCCCATC
ATCTTCCTTCCATGTGCTACAACGTCTACTCGCTGGCCTTCTGATCCGTGCGGTGGCCGGAGC
GCAGAGCTGGCCTGTGACCAGGAGGCGGGCGCGCTCTACGTGATCCAGGAGGGCCTGGAGAA
CACGGGCTGCACGCTGGTCTTCTACTGCTCTACTACTTCGGCATGGCCAGCTCGCTCTGGTGG
GTGGTCTTGACGCTCACCTGGTTCCTGGCTGCCGGGAAGAAATGGGGCCACGAGGCCATCGAG
GCCACGGCAGCTATTTCCACATGGCTGCCTGGGGCCTGCCCGCGCTCAAGACCATCGTCATCC
TGACCCTGCGCAAGGTGGCGGGTGATGAGCTGACTGGGCTTTGCTACGTGGCCAGCACGGATG
CAGCAGCGCTCACGGGCTTCGTGCTGGTGCCCTCTCTGGCTACCTGGTGCTGGGCAGTAGTTT
CCTCCTGACCGGCTTCGTGGCCCTCTTCCACATCCGCAAGATCATGAAGACGGGCGGCACCAAC
ACAGAGAAGCTGGAGAAGCTCATGGTCAAGATCGGGGTCTTCTCCATCCTCTACACGGTGCCCG
CCACCTGCGTCATCGTTTGCTATGTCTACGAACGCCTCAACATGGACTTCTGGCGCCTTCGGGCC
ACAGAGCAGCCATGCGCAGCGGCCGCGGGGCCCGGAGGCCGAGGGACTGCTCGCTGCCAGG
GGGCTCGGTGCCACCGTGGCGGTCTTCATGCTCAAAATTTTCATGTCACTGGTGGTGGGGATC
ACCAGCGGCGTCTGGGTGTGGAGCTCCAAGACTTTCAGACCTGGCAGAGCCTGTGCTACCGCA
AGATAGCAGCTGGCCGGGGCCCCGGGCCAAGGCCTGCCGCGCCCCCGGGAGCTACGGACGTGGCA
CGCACTGCCACTATAAGGCTCCCACCGTGGTCTTGACATGACTAAGACGGACCCCTCTTTGGA
GAACCCACACACCTCTAGCCACACAGGCCTGGCGCGGGGTGGCTGCTGCCCCCTCCTTGCCCT
CCACGCCCTGCCCCCTGCATCCCCTAGAGACAGCTGACTAGCAGCTGCCAGCTGTCAAGGTCA
GGCAAGTGAGCACCGGGGACTGAGGATCAGGGCGGGACCCCGTGAGGCTCATTAGGGGAGAT
GGGGGTCTCCCCTAATGCGGGGGCTGGACCAGGCTGAGTCCCCACAGGGTCTAGTGGAGGAT
GTGGAGGGGCGGGGCAGAGGGGTCCAGCCGAGTTTATTTAATGATGTAATTTATTGTTGCGTT
CCTCTGGAAGCTGTGACTGGAATAAACCCCGCGTGCGCACTGCTGATCCTCTCTGGCTGGGAAG
GGGAAGGTAGGAGGTGAGGC

Figure 39

ACACGTCCAACGCCAGCATGCAGCGCCCCGGGCCCCCGCCTGTGGCTGGTCTCGCAGGTGATGG
GCTCGTGCGCCGCCATCAGCTCCATGGACATGGAGCGCCCGGGCGACGGCAAATGCCAGCCCA
TCGAGATCCCGATGTGCAAGGACATCGGCTACAACATGACTCGTATGCCAACCTGATGGGCC
ACGAGAACCAGCGCGAGGCAGCCATCCAGTTGCACGAGTTCGCGCCGCTGGTGGAGTACGGCT
GCCACGGCCACCTCCGCTTCTTCCTGTGCTCGCTGTACGCGCCGATGTGCACCGAGCAGGTCTC
TACCCCATCCCGCCTGCCGGGTGCTGTGCGAGCAGGCCCGGCTCAAGTGCTCCCCGATTATG
GAGCAGTTCAACTTCAAGTGGCCCGACTCCCTGGACTGCCGGA AACTCCCCAACAAAGAACGAC
CCCAACTACCTGTGCATGGAGGCGCCCAACAACGGCTCGGACGAGCCACCCGGGGCTCGGGC
CTGTTCCCGCCGCTGTTCCGGCCGCGAGCGGCCCCACAGCGCGCAGGAGCACCCGCTGAAGGAC
GGGGGCCCCGGGCGCGGCGGCTGCGACAACCCGGGCAAGTTCCACCAGTGGAGAAGAGCGC
GTCGTGCGCGCCGCTCTGCACGCCCCGGCGTGAGTACTGGAGCCGCGAGGACAAGCGCTT
CGCAGTGGTCTGGCTGGCCATCTGGGCGGTGCTGTGCTTCTTCTCCAGCGCCTTCACCGTGCTCA
CCTTCCTCATGACCCGGCCCGCTTCCGCTACCCGAGCGCCCCATCATCTTCTCTCCATGTGC
TACTGCGTCTACTCCGTGGGCTACCTCATCCGCTCTTCGCCGCGCGCGAGAGCATCGCCTGCG
ACCGGGACAGCGGCCAGCTCTATGTATCCAGGAGGACTGGAGAGCACCGGCTGCACGCTGG
TCTTCCTGGTCTCTACTACTTCGGCATGGCCAGCTCGCTGTGGTGGTGGTCTCACGCTCACC

TGGTTCCTGGCCGCCGCAAGAAGTGGGGCCACGAGGCCATCGAAGCCAACAGCAGCTACTTC
CACCTGGCAGCCTGGGCCATCCCGGCGGTGAAGACCATCCTGATCCTGGTCATGCGCAGGGTG
GCGGGGACGAGCTACCGGGGTCTGCTACGTGGGCAGCATGGACGTCAACGCGCTCACCGGC
TTCGTGCTCATTCCCCTGGCCTGCTACCTGGTCATCGGCACGTCCTTCATCCTCTCGGGCTTCGT
GGCCCTGTTCCACATCCGGAGGGTGATGAAGACGGGCGGCGAGAACACGGACAAGCTGGAGA
AGCTCATGGTGCGTATCGGGCTCTTCTCTGTGCTGTACACCGTGCCGGCCACCTGTGTGATCGCC
TGCTACTTTTACGAACGCCTCAACATGGATTACTGGAAGATCCTGGCGGCGCAGCACAAAGTGCA
AAATGAACAACCAGACTAAAACGCTGGACTGCCTGATGGCCGCTCCATCCCCGCCGTGGAGA
TCTTCATGGTGAAGATCTTTATGCTGCTGGTGGTGGGGATCACCAGCGGGATGTGGATTTGGAC
CTCCAAGACTCTGCAGTCCTGGCAGCAGGTGTGCAGCCGTAGGTAAAGAAGAAGAGCCGGAG
AAAACCGGCCAGCGTGATCACCAGCGGTGGGATTTACAAAAAGCCAGCATCCCCAGAAAAC
TCACCACGGGAAATATGAGATCCCTGCCAGTCGCCACCTGCGTGTGAACAGGGCTGGAGGG
AAGGGCACAGGGGCGCCCGAGCTAAGATGTGGTGCTTTTCTTGTTGTGTTTTCTTTCTTCTT
CTTCTTTTTTTTTTTTTTATAAAAGCAAAAGAGAAATACATAAAAAAGTGTTTACCCTGAAATTC
AGGATGCTGTGATACACTGAAAGGAAAAATGTACTTAAAGGGTTTTGTTTTGTTTTGGTTTTCC
AGCGAAGGGAAGCTCCTCCAGTGAAGTAGCCTCTTGTTGTAACATAATTTGTGTTAAAGTAGTTGA
TTCAGCCCTCAGAAGAAAACTTTTGTAGAGCCCTCCGTAAATATACATCTGTGTATTTGAGTT
GGCTTTGCTACCCATTTACAAATAAGAGGACAGATAACTGCTTTGCAAATTCAAGAGCCTCCCC
TGGGTTAACAATGAGCCATCCCCAGGGCCACCCCCAGGAAGGCCACAGTGCTGGGCGGCAT
CCCTGCAGAGGAAAGACAGGACCCGGGGCCCGCCTCACACCCAGTGAGTTTGGAGTTGCTTA
AAATAGACTCTGGCCTTACCAATAGTCTCTCTGCAAGACAGAAACCTCCATCAAACCTCACAT
TTGTGAACCTAAACGATGTGCAATACATTTTTTCTCTTTCTTGAATAAAAAAGAGAAACAA
GTATTTTGTATATATAAAGACAACAAAAGAAATCTCCTAACAAAAGAACTAAGAGGCCCCAGC
CCTCAGAAACCTTCAGTGCTACATTTTGTGGCTTTTTAATGGAAACCAAGCCAATGTTATAGA
CGTTTGGACTGATTTGTGGAAAGGAGGGGGGAAGAGGGAGAAGGATCATCAAAGTTACCCA
AAGGGCTTATTGACTCTTTCTATTGTAAACAAATGATTTCCACAAACAGATCAGGAAGCACTA
GGTTGGCAGAGACACTTTGTCTAGTGTATTCTTTCACAGTGCCAGGAAAGAGTGGTTTCTGCG
TGTGTATATTTGTAATATATGATATTTTCATGCTCCACTATTTTATTAATAAAATATGTTCT
TTAAAAAA

Figure 40

CCTGCAGCCTCCGGAGTCAGTGCCGCGCGCCCGCCGCCCCGCGCCTTCTGCTCGCCGCACCTC
CGGGAGCCGGGGCGCACCCAGCCCGCAGCGCCGCTCCCCGCCCCGCGCCTCCGACCGCAG
GCCGAGGGCCGCCACTGGCCGGGGGGACCGGCCAGCAGCTTGCGGCCGCGGAGCCGGGCAAC
GCTGGGGACTGCGCCTTTGTCCCGGAGGTCCCTGGAAGTTTGGCGCAGGACGCGCGCGGGG
AGGCGGCGGAGGCGACCCCGACGTCGCGGAGAACAGGGCGCAGAGCCGGCATGGGCATCGGG
CGCAGCGAGGGGGCGCGCGGGCCCTGGGCGTGCTGCTGGCGCTGGGCGCGGCGCTTCTG
GCCGTGGGCTCGGCCAGCGAGTACGACTACGTGAGCTTCCAGTCGGACATCGGCCCGTACCAG
AGCGGGCGCTTCTACACCAAGCCACCTCAGTGCGTGGACATCCCCGCGGACCTGCGGCTGTGCC
ACAACGTGGGCTACAAGAAGATGGTGCTGCCAACCTGCTGGAGCACGAGACCATGGCGGAGG
TGAAGCAGCAGGCCAGCAGCTGGGTGCCCTGCTCAACAAGAACTGCCACGCCGGGACCCAGG
TCTTCTCTGCTCGCTCTTCGCGCCCGTCTGCCTGGACCGGCCATCTACCCGTGTGCTGGCTC
TGCGAGGCCGTGCGCGACTCGTGCGAGCCGTCATGCAGTTCTTCGGCTTCTACTGGCCCGAGA
TGCTTAAGTGTGACAAGTCCCAGAGGGGGACGTCTGCATCGCCATGACGCCGCCCAATGCCAC
CGAAGCCTCCAAGCCCCAAGGCACAACGGTGTGTCTCCCTGTGACAACGAGTTGAAATCTGA
GGCCATCATTGAACATCTCTGTGCCAGCGAGTTTGCAGTGAAGATGAAAATAAAGAAGTGAA
AAAAGAAAATGGCGACAAGAAGATTGTCCCAAGAAGAAGAAGCCCTGAAGTTGGGGCCCA
TCAAGAAGAAGGACCTGAAGAAGCTTGTGCTGTACCTGAAGAATGGGGCTGACTGTCCCTGCC
ACCAGCTGGACAACCTCAGCCACCACTTCTCATCATGGGCCGCAAGGTGAAGAGCCAGTACTT
GCTGACGGCCATCCACAAGTGGGACAAGAAAAACAAGGAGTTCAAAAACTTCATGAAGAAAA
TGAAAAACCATGAGTGCCCCACCTTTCAGTCCGTGTTTAAAGTATTCTCCCGGGGGCAGGGTGG
GGAGGGAGCCTCGGGTGGGGTGGGAGCGGGGGGACAGTGCCCGGGAACCCGTGGTCAACA
CACGCACTGCCCTGTCAAGTAGTGACATTGTAATCCAGTCGGCTTGTCTTGCAGCATTCCC

CCCTTTCCCTCCATAGCCACGCTCCAAACCCCAAGGGTAGCCATGGCCGGGTAAAGCAAGGGCC
ATTTAGATTAGGAAGGTTTTTAAGATCCGCAATGTGGAGCAGCAGCCACTGCACAGGAGGAGG
TGACAAACCATTTCCAACAGCAACACAGCCACTAAAAACAAAAAGGGGGATTGGGCGGAAA
GTGAGAGCCAGCAGCAAAAACTACATTTTGCACCTTGTGGTGTGGATCTATTGGCTGATCTAT
GCCTTTCAACTAGAAAATTCTAATGATTGGCAAGTCACGTTGTTTTTCAGGTCCAGAGTAGTTTCT
TTCTGTCTGCTTTAAATGGAAACAGACTCATACCACACTTACAATTAAGGTCAAGCCCAGAAAG
TGATAAGTGCAGGGAGGAAAAGTGCAAGTCCATTATCTAATAGTGACAGCAAAGGGACCAGGG
GAGAGGCATTGCCTTCTCTGCCCACAGTCTTTCCGTGTGATTGTCCTTTGAATCTGAATCAGCCAG
TCTCAGATGCCCCAAAGTTTCGGTTCCTATGAGCCCCGGGGCATGATCTGATCCCCAAGACATGT
GGAGGGGCAGCCTGTGCCTGCCTTTGTGTGAGAAAAAGGAAACCACAGTGAGCCTGAGAGAGA
CGGCGATTTTCGGGCTGAGAAGGCAGTAGTTTTCAAAACACATAGTTA

Figure 41

GAATTCGTTACGCCTGGTTAAGTCCAAGCTGGCTCATTCTGCTCCCCCGGGTCGGAGCCCCCG
GAGCTGCGCGCGGGCTTGACAGCGCCTCGCCCGCGCTGTCTCCCGGTGTCCCGCTTCTCCGCGC
CCCAGCCGCGGGCTGCCAGCTTTTCGGGGCCCCGAGTCGCACCCAGCGAAGAGAGCGGGGCCG
GGACAAGCTCGAACTCCGGCCGCCTCGCCCTTAACCAGCTCCGTCCCTCTACCCCTAGGGGTC
GCGCCACGATGCTGCAGGGCCCTGGCTCGCTGCTGCTCTTCTCGCCTCGCACTGCTGCCT
GGGCTCGGCGCGCGGGCTCTTCTCTTTGGCCAGCCCCGACTTCTCTACAAGCGCAGCAATTGC
AAGCCCATCCCGGCCAACCTGCAGCTGTGCCACGGCATCGAATACCAGAACATGCGGCTGCCC
AACCTGCTGGGCCACGAGACCATGAAGGAGGTGCTGGAGCAGGCCGGCGCTTGGATCCCGCTG
GTCATGAAGCAGTGCCACCCGGACACCAAGAAGTTCCTGTGCTCGCTCTTCGCCCCCGTCTGCC
TCGATGACCTAGACGAGACCATCCAGCCATGCCACTCTCGNTGCGTGAGGTGAAGGATCGCT
GCGCCCCGCTCATGTCCGCCTTCCCCTGGCCCCGACATGCTTGAGTGCGACCGTTTCCCCCAGGA
CAACGACCTTTGCATCCCCCTCGCTAGCAGCGACCACCTCCTGCCAGCCACCGAGGAAGCTCCA
AAGGTATGTGAAGCCTGAAAAATAAAAATGATGATGACAACGACATAATGGAACGCTTTGT
AAAAATGATTTTGCCTGAAAAATAAAGTGAAGGAGATAACCTACATCAACCGT

Figure 42

CCGGGTGCGAGCCCCCGGAGCTGCGCGCGGGCTTGACAGCGCCTCGCCCGCGCTGTCTCCCGGTGTCCC
GCTTCTCCGCGCCCCAGCCGCGGGCTGCCAGCTTTTCGGGGCCCCGAGTCGCACCCAGCGAAGAGAGCGG
GCCCCGGACAAGCTCGAACTCCGGCCGCCTCGCCCTTCCCCGGCTCCGCTCCCTCTGCCCCCTCGGGGTC
GCGCGCCACGATGCTGCAGGGCCCTGGCTCGCTGCTGCTGCTCTTCTCGCCTCGCACTGCTGCCTGGG
CTCGGCGCGCGGGCTCTTCTCTTTGGCCAGCCCCGACTTCTCTACAAGCGCAGCAATTGCAAGCCCATC
CCTGCCAACCTGCAGCTGTGCCACGGCATCGAATACCAGAACATGCGGCTGCCAACCTGCTGGGCCACG
AGACCATGAAGGAGGTGCTGGAGCAGGCCGGCGCTTGGATCCCGCTGGTCATGAAGCAGTGCCACCCGGA
CACCAAGAAGTTCTGTGCTCGCTCTTCGCCCCCGTCTGCCTCGATGACCTAGACGAGACCATCCAGCCA
TGCCACTCGCTCTGCGTGAGGTGAAGACCGCTGCGCCCCGGTTCATGTCCGCCTTCGGCTTCCCCTGGC
CCGACATGCTTGAGTGCGACCGTTTCCCCCAGGACAACGACCTTTGCATCCCCCTCGCTAGCAGCGACCA
CCTCCTGCCAGCCACCGAGGAAGCTCCAAAGGTATGTGAAGCCTGCAAAAATAAAAATGATGATGACAAC
GACATAATGGAACGCTTTGTAAAAATGATTTTGCCTGAAAATAAAGTGAAGGAGATAACCTACATCA
ACCGAGATACCAAAATCATCCTGGAGACCAAGAGCAAGACCATTTACAAGCTGAACGGTGTGTCCGAAAG
GGACCTGAAGAAATCGGTGCTGTGGCTCAAAGACAGCTTGCAGTGCACCTGTGAGGAGATGAACGACATC
AACGCGCCCTATCTGGTCATGGGACAGAAACAGGGTGGGGAGCTGGTGATCACCTCGGTGAAGCGGTGGC
AGAAGGGGCAGAGAGAGTTCAAGCGCATCTCCCGCAGCATCCGCAAGCTGCAGTGCTAGTCCCGGCATCC
TGATGGCTCCGACAGGCCTGCTCCAGAGCACGGCTGACCATTTCTGCTCCGGGATCTCAGCTCCCGTTCC
CCAAGCACACTCCTAGCTGCTCCAGTCTCAGCCTGGGCAGCTTCCCCCTGCCTTTTGCACGTTTGCATCC
CCAGCATTTCTGAGTTATAAGGCCACAGGAGTGATAGCTGTTTTACCTAAAGGAAAAGCCCACCCGA
ATCTTGTAAGAAATATTCAAACATAAATAATCATGAATATTTTTATGAAGTTT

Figure 43

36/41

ACGGGGCCTGGGCGGSAGGGGCGGTGGCTGGAGCTCGGTAAAGCTCGTGGGACCCCATTTGGGG
GAATTTGATCCAAGGAAGCGGTGATTGCCGGGGGAGGAGAAGCTCCCAGATCCTTGTGTCCAC
TTGCAGCGGGGAGGCGGAGACGCGGAGCGGGCCTTTTGGCGTCCACTGCGCGGCTGCACCCT
GCCCCATCTGCCGGGATCATGGTCTGCGGCAGCCCGGAGGGATGCTGCTGCTGCGGGCCGG
GCTGCTTGCCCTGGCTGCTCTCTGCCTGCTCCGGGTGCCCGGGGCTCGGGCTGCAGCCTGTGAG
CCCGTCCGCATCCCCCTGTGCAAGTCCCTGCCCTGGAACATGACTAAGATGCCCAACCACTGC
ACCACAGCACTCAGGCCAACGCCATCCTGGCCATCGAGCAGTTTGAAGGTCTGCTGGGCACCC
ACTGCAGCCCCGATCTGCTCTTCTTCTCTGTGCCATGTACGCGCCCATCTGCACCATTGACTTC
CAGCACGAGCCCATCAACCCCTGTAAAGTCTGTGTGCGAGCGGGCCCGGCAGGGCTGTGAGCCC
ATACTCATCAAGTACCGCCACTCGTGGCCGGAGAACCTGGCCTGCGAGGAGCTGCCAGTGTAC
GACAGGGGCGTGTGCATCTCTCCCGAGGCCATCGTTACTGCGGACGGAGCTGATTTTCCTATGG
ATTCTAGTAACGAAACTGTAGAGGGGCAAGCAGTGAACGCTGTAAATGTAAGCCTATTAGAG
CTACACAGAAGACCTATTTCCGGAACAATTACAACATATGTCATTTCGGGCTAAAGTTAAAGAGAT
AAAGACTAAGTGCCATGATGTGACTGCAGTAGTGGAGGTGAAGGAGATTCTAAAGTCTCTCT
GGTAAACATTCACGGGACACTGTCAACCTCTATACCAGCTCTGGCTGCCTCTGCCCTCCACTT
AATGTTAATGAGGAATATATCATCATGGGCTATGAAGATGAGGAACGTTCCAGATTACTCTTGG
TGGAAGGCTCTATAGCTGAGAAGTGGAAGGATCGACTCGGTAAAAAAGTTAAGCGCTGGGATA
TGAAGCTTCGTCACTTTGGACTCAGTAAAAGTGATTCTAGCAATAGTGATTCCACTCAGAGTCA
GAAGCTGGCAGGAACCTGAACCCCCGCAAGCACGCAACTAAATCCCGAAATACAAAAAGTA
ACACAGTGGACTTCCTATTAAGACTTACTTGCATTGCTGGACTAGCAAAGGAAAAATTGCACTAT
TGCACATCATATTCTATTGTTTACTATAAAAATCATGTGATAACTGATTATTACTTCTGTTTCTCT
TTTGGTTTCTGCTTCTCTTCTCTCAACCCCTTTGTAATGGTTTGGGGGCAGACTCTTAAGTATA
TTGTGAGTTTCTATTCTACTAATCATGAGAAAACTGTTCTTTTGCAATAATAATAAATTAAC
ATGCTGTTA

Figure 44

CAGCGGCCGCTGAATTCTAGGGCGGGTTCGCGCCCCGAAGGCTGAGAGCTGGCGCTGCTCGTG
CCCTGTGTGCCAGACGGCGGAGCTCCGCGGCCGGACCCCGCGGCCCGCTTTGCTGCCGACTGG
AGTTTGGGGGAAGAACTCTCCTGCGCCCCAGAAGATTTCTTCTCGGCGAAGGGACAGCGAA
AGATGAGGGTGGCAGGAAGAGAAGGCGCTTTCTGTCTGCCGGGTGCGAGCGCGAGAGGGCA
GTGCCATGTTCTCTCCATCCTAGTGGCGCTGTGCCTGTGGCTGCACCTGGCGCTGGGCGTGC
CGGCGCGCCCTGCGAGGCGGTGCGCATCCCTATGTGCCGGCACATGCCCTGGAACATCACGCG
GATGCCCAACCACCTGCACCACAGCACGACGAGGAACGCCATCCTGGCCATCGAGCAGTACGA
GGAGCTGGTGGACGTGAAGTGCAGCGCGTGTGCGCTTCTTCTTCTGTGCCATGTACGCGCCC
ATTTGCACCCCTGGAGTTCTCTGCACGACCCCTATCAAGCCGTGCAAGTCCGTGTGCCAACGCGCGC
GCGACGACTGCGAGCCCCCTCATGAAGATGTACAACCACAGCTGGCCCCGAAAGCCTGGCCTGCG
ACGAGCTGCCTGTCTATGACCGTGGCGTGTGCATTTGCGCTGAAGCCATCGTCACGGACCTCCC
GGAGGATGTTAAGTGGATAGACATCACACCAGACATGATGGTACAGGAAAGGCCTCTTGATGT
TGACTGTAAACGCCTAAGCCCCGATCGGTGCAAGTGTAAAAAGGTGAAGCCAACCTTTGGCAAC
GTATCTCAGCAAAAACTACAGCTATGTTATTATGCCCCAAATAAAAGCTGTGCAGAGGAGTGG
CTGCAATGAGGTACAACGGTGGTGGATGTAAAAGAGATCTTCAAGTCTCATACCCATCCCT
CGAACTCAAGTCCCGCTCATTACAAATTCTTCTTGCCAGTGTCCACACATCCTGCCCCATCAAG
ATGTTCTCATCATGTGTTACGAGTGGCGTTCAAGGATGATGCTTCTTGAAAATTGCTTAGTTGAA
AAATGGAGAGATCAGCTTAGTAAAAGATCCATACAGTGGGAAGAGAGGCTGCAGGAACAGCG
GAGAACAGTTCAGGACAAGAAGAAAACAGCCGGGCGCACCAAGTCGTAGTAATCCCCCAAACC
AAAGGGAAGCCTCCTGCTCCCAAACCAGCCAGTCCCAAGAAGAACATTAAAACTAGGAGTGC
CCAGAAGAGAACAAACCCGAAAAGAGTGTGAGCTAACTAGTTTCCAAAGCGGAGACTTCCGAC
TTCCTTACAGGATGAGGCTGGGCATTGCCTGGGACAGCCTATGTAAGGCCATGTGCCCTTGCC
CTAACAACCTCACTGCAGTGTCTTTCATAGACACATCTTGCAGCATTTTTCTTAAGGCTATGCTTC
AGTTTTTCTTTGTAAGCCATCACAAGCCATAGTGGTAGGTTGCCCTTTGGTACAGAAAGGTGAG
TTAAAGCTGGTGGAAAAGGCTTATTGCATTGCATTAGAGTAACCTGTGTGCATACTCTAGAAG
AGTAGGGAAAATAATGCTTGTTACAATTCGACCTAATATGTGCATTGTAAATAAATGCCATAT
TTCAAACAAAACACGTAATTTTTTACAGTATGTTTTATTACCTTTTGATATCTGTTGTTGCAAT
GTTAGTGATGTTTTAAATGTGATGAAAATATAATGTTTTTAAGAAGGAACAGTAGTGGAATGA
ATGTTAAAGATCTTTATGTGTTTATGGTCTGCAGAAGGATTTTGTGATGAAAGGGGATTTTTT

37/41

GAAAAATTAGAGAAGTAGCATATGGAAAATTATAATGTGTTTTTTTACCAATGACTTCAGTTTC
TGTTTTTAGCTAGAAACTTAAAAACAAAAATAATAATAAGAAAAATAAATAAAAAGGAGAGG
CAGACAATGTCTGGATTCTGTTTTTTGGTTACCTGATTTCATGATCATGATGCTTCTTGTCAA
CACCTCTTAAGCAGCACCAGAAACAGTGAGTTTGTCTGTACCATTAGGAGTTAGGTACTAATT
AGTTGGCTAATGCTCAAGTATTTTATACCCACAAGAGAGGTATGTCACTCATCTTACTTCCAG
GACATCCACCCTGAGAATAATTTGACAAGCTTAAAAATGGCCTTCATGTGAGTGCCAAATTTTG
TTTTTCTTCATTTAAATATTTTCTTTGCCTAAATACATGTGAGAGGAGTTAAATATAAATGTACA
GAGAGGAAAGTTGAGTTCCACCTCTGAAATGAGAATTACTTGACAGTTGGGATACTTTAATCAG
AAAAAAGAACTTATTTGCAGCATTTTATCAACAAATTTTATAATTGTGGACAATTGGAGGCAT
TTATTTTAAAAACAATTTTATTGGCCTTTTGCTAACACAGTAAGCATGTATTTTATAAGGCATT
CAATAAATGCACAACGCCCAAAGGAAATAAAATCCTATCTAATCCTACTCTCCACTACACAGA
GGTAATCACTATTAGTATTTTGGCATATTATTCTCCAGGTGTTTGCTTATGCACCTATAAAAATGA
TTTGAACAAATAAACTAGGAACCTGTATACATGTGTTTTCATAACCTGCCTCTTGCTTGGCCC
TTTATTGAGATAAGTTTTCTGTCAAGAAAGCAGAAACCATCTCATTCTAACAGCTGTGTTATA
TTCCATAGTATGCATTACTCAACAACTGTTGTGCTATTGGATACTTAGGTGGTTTCTTCACTGA
CAATACTGAATAAACATCTCACCGGAATTC

Figure 45

AAGCTTGATATCGAATTCGCGGCCGCGCTCGACGGGAGGCGCCAGGATCAGTCGGGGCACCCGC
AGCGCAGGCTGCCACCCACCTGGGCGACCTCCGCGGCGGCGGCGGCGGCGGCTGGGTAGAGTC
AGGGCCGGGGGCGCACGCCGAACACCTGGGCGCGCGGGCACCGAGCGTCGGGGGGCTGCGC
GGCGCGACCCTGGAGAGGGCGCAGCCGATGCGGGCGGCGGCGGCGGCGGCGGGGGCGTGCGGAC
GGCCGCGCTGGCGCTGCTGCTGGGGGCGCTGCACTGGGCGCGGCGGCGGCTGCGAGGAGTACGA
CTACTATGGCTGGCAGGCCGAGCCGCTGCACGGCCGCTCCTACTCCAAGCCGCCGAGTGCCTT
GACATCCCTGCCGACCTGCCGCTCTGCCACACGGTGGGCTACAAGCGCATGCGGCTGCCCAACC
TGCTGGAGCACGAGAGCCTGGCCGAAGTGAAGCAGCAGGCGAGCAGCTGGCTGCCGCTGCTGG
CCAAGCGCTGCCACTCGGATACGCAGGTCTTCTGTGCTCGCTCTTTGCGCCCGTCTGTCTCGAC
CGGCCCATCTACCCGTGCCGCTCGCTGTGCGAGGCCGTGCGCGCCGGCTGCGCGCCGCTCATGG
AGGCCTACGGCTTCCCCTGGCCTGAGATGCTGCACTGCCACAAGTTCCCCCTGGACAACGACCT
CTGCATCGCCGTGCAGTTCGGGACCTGCCCCGCCACCGCGCCTCCAGTGACCAAGATCTGCGCC
CAGTGTGAGATGGAGCACAGTGCTGACGGCCTCATGGAGCAGATGTGCTCCAGTGACTTTGTG
GTCAAAATGCGCATCAAGGAGATCAAGATAGAGAATGGGGACCGGAAGCTGATTGGAGCCCA
GAAAAAGAAGAAGCTGCTCAAGCCGGGCCCCCTGAAGCGCAAGGACACCAAGCGGCTGGTGC
TGCACATGAAGAATGGCGCGGGCTGCCCCCTGCCACAGCTGGACAGCCTGGCGGGCAGCTTCC
TGGTCATGGGCCGCAAAGTGGATGGACAGCTGCTGCTCATGGCCGTCTACCGCTGGGACAAGA
AGAATAAGGAGATGAAGTTTGCAGTCAAATTCATGTTCTCCTACCCCTGCTCCCTCTACTACCT
TTCTTCTACGGGGCGGCAGAGCCCCACTGAAGGGCACTCCTCCTTGCCCTGCCAGCTGTGCCTT
GCTTGCCCTCTGGCCCCGCCCAACTTCCAGGCTGACCCGGCCCTACTGGAGGGTGTTTCACG
AATGTTGTTACTGGCACAAGGCCTAAGGGATGGGCACGGAGCCCAGGCTGTCTTTTTGACCCA
GGGGTCTGGGGTCCCTGGGATGTTGGGCTTCTCTCAGGAGCAGGGCTTCTTCATCTGGGT
GAAGACCTCAGGGTCTCAGAAAGTAGGCAGGGGAGGAGAGGGTAAGGGAAAGGTGGAGGGGC
TCAGGGCACCCCTGAGGCGGAGGTTTCAGAGTAGAAGGTGATGTCAGCTCCAGCTCCCCCTGTGC
GGTGGTGGGGCCTCACCTTGAAGAGGGAAGTCTCAATATTAGGCTAAGCTATTTGGGAAAGTTC
TCCCCACCGCCCCTGTACGCGTCATCTAGCCCCCTTAGGAAAGGAGTTAGGGTCTCAGTGCC
TCCAGCCACACCCCCTGCCTTCCCCAGCTTGCCCATTTCCCTGCCCAAGGCCAGAGCTCCCC
CAGACTGGAGAGCAAGCCCAGCCCAGCCTCGGCATAGACCCCCTTCTGGTCCGCCCGTGGCTCG
ATCCCCGGGATTCATTCTCAGCCTCTGCTTCTCCCTTTTATCCCAATAAGTTATTGCTACTGCTG
TGAGGCCATAGGTAAGTACACAACCAATACATGCAGGGTTGGGTTTTCTAATTTTTTAACTTTTT
AATTAAATCAAAGTTCGACGCGCGGCCGCGGAATTCCTGCAGCCCGGGGGATCCCCGGGTACC
GAGCTCGAATTC

Figure 46

38/41

ATGCATCTCCTCTTATTTTCAGCTGCTGGTACTCCTGCCTCTAGGAAAGACCACACGGCACCAGG
ATGGCCGCCAGAATCAGAGTTCTCTTTCCCGTACTCCTGCCAAGGAATCAAAGAGAGCTTCC
CACAGGCAACCATGAGGAAGCTGAGGAGAAGCCAGATCTGTTTGTGCGAGTGCCACACCTTGT
AGCCACAGCCCTGCAGGGGAAGGCCAGAGGCAGAGAGAGAAGATGCTGTCCAGATTGCGCA
GGTTCTGGAAGAAGCCTGAGAGAGAAATGCATCCATCCAGGGACTCAGATAGTGAGCCCTTCC
CACCTGGGACCCAGTCCCTCATCCAGCCGATAGATGGAATGAAAATGGAGAAATCTCCTCTTCG
GGAAGAAGCCAAGAAATTTCTGGCACCCTTCATGTTTCAAAAACTCCGGCTTCTCAGGGGGT
CATCTTGGCCATCAAAAAGCCATGAAGTACATTGGGAGACCTGCAGGACAGTGCCCTTCAGCCA
GACTATAACCCACGAAGGCTGTGAAAAAGTAGTTGTTTCAAGAACCTTTGCTTTGGGAAATGC
GGGTCTGTTTCAATTTTCTGGAGCCGCGCAGCACTCCCATACCTCCTGCTCTCACTGTTTGCCTGC
CAAGTTACACGATGCACCTGCCACTGAACTGCACTGAACTTTTCTCCGTGATCAAGGTGGTG
ATGCTGGTGGAGGAGTGCCAGTGCAAGGTGAAGACGGAGCATGAAGATGGACACATCCTACAT
GCTGGCTCCCAGGATTCTTTATCCCAGGAGTTTCAGCTTGA

Figure 47

CGGCACGGTTTTCGTGGGGACCCAGGCTTGCAAAGTGACGGTCATTTTCTCTTTCTTTCTCCCTCT
TGAGTCCTTCTGAGATGATGGCTCTGGGCGCAGCGGGAGCTACCCGGGTCTTTGTCGCGATGGT
AGCGGCGGCTCTCGGCGGCCACCCTCTGCTGGGAGTGAGCGCCACCTTGAACCTCGGTTCTCAAT
TCCAACGCTATCAAGAACCTGCCCCACCGCTGGGCGGCGCTGCGGGGCACCCAGGCTCTGCA
GTCAGCGCCGCGCCGGGAATCCTGTACCCGGGCGGGAATAAGTACCAGACCATTGACAACCTAC
CAGCCGTACCCGTGCGCAGAGGACGAGGAGTGCGGCACTGATGAGTACTGCGCTAGTCCCACC
CGCGGAGGGGACGCAGGCGTGCAAATCTGTCTCGCCTGCAGGAAGCGCCGAAAACGCTGCATG
CGTCACGCTATGTGCTGCCCCGGGAATTACTGCAAAAATGGAATATGTGTGTCTTCTGATCAAA
ATCATTTCCGAGGAGAAATTGAGGAAACCATCACTGAAAGCTTTGGTAATGATCATAGCACCTT
GGATGGGTATTCCAGAAGAACCACCTTGTCTTCAAAAATGTATCACACCAAAGGACAAGAAGG
TTCTGTTTGTCTCCGGTCATCAGACTGTGCCTCAGGATTGTGTTGTGCTAGACACTTCTGGTCCA
AGATCTGTAAACCTGTCCTGAAAGAAGGTCAAGTGTGTACCAAGCATAGGAGAAAAGGCTCTC
ATGGACTAGAAATATTCCAGCGTTGTTACTGTGGAGAAGGTCTGTCTTGCCGGATACAGAAAGA
TCACCATCAAGCCAGTAATTCTTCTAGGCTTCACACTTGTGAGAGACACTAAACCAGCTATCCA
AATGCAGTGAACCTCTTTTATATAATAGATGCTATGAAAACCTTTTATGACCTTCATCAACTCAA
TCCTAAGGATATACAAGTTCTGTGGTTTTAGTTAAGCATTCCAATAACACCTTCCAAAAACCTG
GAGTGTAAGAGCTTTGTTTCTTTATGGAACCTCCCTGTGATTGCAGTAAATTACTGTATTGTAAA
TTCTCAGTGTGGCACTTACCTGTAAATGCAATGAACTTTTAATTATTTTTCTAAAGGTGCTGCA
CTGCCTATTTTCTCTTGTATGTAAATTTTGTACACATTGATTGTTATCTTGACTGACAAATA
TTCTATATTGAAGTAAAGTAAATCAATTTTCTAGCTTATAGTTCTTAAAAGCATAACCTTTACCCCA
TTTAATTCTAGAGTCTAGAACGCAAGGATCTCTTGAATGACAAATGATAGGTACCTAAAATGT
AACATGAAAATACTAGCTTATTTTCTGAAATGTACTATCTTAATGCTTAAATTATTTTCCCTTT
AGGCTGTGATAGTTTTTGAATAAAATTTAACATTTAATATCATGAAATGTTATAAGTAGACAT

Figure 48

GCGGGTCTCGCTTGGGTTCCGCTAATTTCTGTCTGAGGCGTGAGACTGAGTTCATAGGGTCTT
GGGTCCCCGAACCAGGAAGGGTTGAGGGAACACAATCTGCAAGCCCCCGGACCCAAGTGAGG
GGCCCCGTGTTGGGGTCTCCCTCCCTTTGCATTCCCACCCCTCCGGGCTTTGCGTCTTCTGGG
GACCCCTCGCCGGGAGATGGCCGCGTTGATGCGGAGCAAGGATTGCTCCTGCTGCCTGCTCCT
ACTGGCCGCGGTGCTGATGGTGGAGAGCTCACAGATCGGCAGTTCGCGGGCCAACTCAACTC
CATCAAGTCTCTCTGGGCGGGGAGACGCCTGGTCAGGCGGCCAATCGATCTGCGGGCATGTAC
CAAGGACTGGCATTGCGCGGCAGTAAGAAGGGCAAAAACCTGGGGCAGGCCCTACCTTGTAGC
AGTGATAAGGAGTGTGAAGTTGGGAGGTATTGCCACAGTCCCCACCAAGGATCATCGGCCTGC
ATGGTGTGTGCGGAGAAAAAAGAAGCGCTGCCACCGAGATGGCATGTGCTGCCCCAGTACCCGC
TGCAATAATGGCATCTGTATCCAGTTACTGAAAGCATCTTAACCCCTCACATCCCGGCTCTGG
ATGGTACTCGGCACAGAGATCGAAACCACGGTCATTACTCAAACCATGACTTGGGATGGCAGA
ATCTAGGAAGACCACACACTAAGATGTACATATAAAAGGGCATGAAGGAGACCCCTGCCTAC
GATCATCAGACTGCATTGAAGGGTTTTGCTGTGCTCGTCATTTCTGGACCAAAATCTGCAAACC

AGTGCTCCATCAGGGGGAAGTCTGTACCAACAACGCAAGAAGGGTTCTCATGGGCTGGAAAT
TTTCCAGCGTTGCGACTGTGCGAAGGGCCTGTCTTGCAAAGTATGGAAAGATGCCACCTACTCC
TCCAAAGCCAGACTCCATGTGTGTCAGAAAATTTGATCACCATTGAGGAACATCATCAATTGCA
GACTGTGAAGTTGTGTATTTAATGCATTATAGCATGGTGGAAAATAAGGTTTCAGATGCAGAAG
AATGGCTAAAATAAGAAACGTGATAAGAATATAGATGATCAC

Figure 49

CTATCACAATGAGACCAACACAGACACGAAGGTTGGAAATAATACCATCCATGTGCACCGAGA
AATTCACAAGATAACCAACAACCAGACTGGACAAATGGTCTTTTCAGAGACAGTTATCACATCT
GTGGGAGACGAAGAAGGCAGAAGGAGCCACGAGTGCATCATCGACGAGGACTGTGGGCCCAG
CATGTACTGCCAGTTTGCCAGCTTCCAGTACACCTGCCAGCCATGCCGGGGCCAGAGGATGCTC
TGCACCCGGGACAGTGAGTGTCTGTGGAGACCAGCTGTGTGTCTGGGGTCACTGCACCAAAATG
GCCACCAGGGGACGAATGGGACCATCTGTGACAACCAGAGGGACTGCCAGCCGGGGCTGTGC
TGTGCCTTCCAGAGAGGCCTGCTGTTCCCTGTGTGCACACCCCTGCCCGTGGAGGGGCGAGCTTT
GCCATGACCCCGCCAGCCGGCTTCTGGACCTCATCACCTGGGAGCTAGAGCCTGATGGAGCCTT
GGACCGATGCCCTTGTGCCAGTGGCCTCCTCTGCCAGCCCCACAGCCACAGCCTGGTGTATGTG
TGCAAGCCGACCTTCGTGGGGAGCCGTGACCAAGATGGGGAGATCCTGCTGCCAGAGAGGTC
CCCGATGAGTATGAAGTTGGCAGCTTCATGGAGGAGGTGCGCCAGGAGCTGGAGGACCTGGAG
AGGAGCCTGACTGAAGAGATGGCGCTGGGGGAGCCTGCGGCTGCCGCCGCTGCACTGCTGGGA
GGGGAAGAGATTTAGATCTGGACCAGGCTGTGGGTAGATGTGCAATAGAAATAGCTAATTTAT
TTCCCCAGGTGTGTGCTTTAGGCGTGGGCTGACCAGGCTTCTTCTACATCTTCTTCCCAGTAAG
TTTCCCTCTGGCTTGACAGCATGAGGTGTTGTGCAATTTGTTTCAGCTCCCCAGGCTGTTCTCCA
GGCTTCACAGTCTGGTGTCTGGGAGAGTCAGGCAGGGTTAAACTGCAGGAGCAGTTTGCCACC
CCTGTCCAGATTATTGGCTGCTTTGCCTCTACCAGTTGGCAGACAGCCGTTTGTCTACATGGCT
TTGATAATTGTTTGGGGGAGGAGATGGAAACAATGTGGAGTCTCCCTCTGATTGGTTTTGGGG
AAATGTGGAGAAGAGTGCCCTGCTTTGCAAACATCAACCTGGCAAAAATGCAACAAATGAATT
TTCCACGCAGTTCTTTCCATGGGCATAGGTAAGCTGTGCCTTCAGCTGTTGCAGATGAAATGTT
TGTTACCCCTGCATTACATGTGTTTATTCATCCAGCAGTGTGCTCAGCTCCTACCTCTGTGCCA
GGGCAGCATTTTCATATCCAAGATCAATTCCTCTCTCAGCACAGCCTGGGGAGGGGGTCAATTG
TTCTCCTCGTCCATCAGGGATCTCAGAGNCTCAGAGACTGCAAGCTGCTTGCCCAAGTCACAC
AGCTAGTGAAGACCAGAGCAGTTTCATCTGGTTGTGACTCTAAGCTCAGTGCTCTCTCCACTAC
CCCACACCAGCCTTGGTGCCACCAAAAGTGCTCCCCAAAAGGAAGGAGAATGGGATTTTTCTTT
TGAGGCATGCACATCTGGAATTAAGGTCAAATAATTCTCACATCCCTCTAAAAGTAACTACT
GTTAGGAACAGCAGTGTCTCACAGTGTGGGGCAGCCGTCCTTCTAATGAAGACAATGATATTG
ACACTGTCCCTCTTTGGCAGTTGCATTAGTAACCTTTGAAAGGTATATGACTGAGCGTAGCATAC
AGGTTAACCTGCAAAACAGTACTTAGTAATTGTAGGGCAGGATTATAAATCAAAATTTGCA
AAATCACTTAGCAGCAACTGAAGACAATTATCAACCACGTGGAGAAAATCAAACCGAGCAGGG
CTGTGTGAAACATGGTTGTAATATGCGACTGCGAACTGAACTCTACGCCACTCCACAAATGA
TGTTTTTCAGGTGTCATGGACTGTTGCCACCATGTATTCATCCAGAGTTCTTAAAGTTTAAAGTTG
CACATGATTGTATAAGCATGCTTTCTTTGAGTTTTAAATTATGTATAAACATAAGTTGCATTTAG
AAATCAAGCATAAATCAC

Figure 50

AGACGACGTGCTGAGCTGCCAGCTTAGTGGAAGCTCTGCTCTGGGTGGAGAGCAGCCTCGCTTT
GGTGACGCACAGTGTCTGGGACCCTCCAGGAGCCCCGGGATTGAAGGATGGTGGCGGCCGTCCT
GCTGGGGCTGAGCTGGCTCTGCTCTCCCTGGGAGCTCTGGTCCTGGACTTCAACAACATCAGG
AGCTCTGCTGACCTGCATGGGGCCGGAAGGGCTCACAGTGCCTGTCTGACACGGACTGCAAT
ACCAGAAAGTTCTGCCTCCAGCCCCGCGATGAGAAGCCGTTCTGTGCTACATGTCGTGGGTTGC
GGAGGAGGTGCCAGCGAGATGCCATGTGCTGCCCTGGGACACTCTGTGTGAACGATGTTTGTAC
TACGATGGAAGATGCAACCCCAATATTAGAAAGGCAGCTTGATGAGCAAGATGGCACACATGC
AGAAGGAACAACCTGGGCACCCAGTCCAGGAAAACCAACCCAAAAGGAAGCCAAGTATTAAGA
AATCACAAGGCAGGAAGGGACAAGAGGGAGAAAGTTGTCTGAGAACTTTTACTGTGGCCCTG

GACTTTGCTGTGCTCGTCATTTTTGGACGAAAATTTGTAAGCCAGTCCTTTTGGAGGGACAGGT
CTGCTCCAGAAGAGGGGCATAAAGACACTGCTCAAGCTCCAGAAATCTTCCAGCGTTGCGACTGT
GGCCCTGGACTACTGTGTGCGAAGCCAATTGACCAGCAATCGGCAGCATGCTCGATTAAGAGTAT
GCCAAAAAATAGAAAAGCTATAAATATTTCAAAATAAAGAAGAATCCACATTGC

Figure 51

AGGCAGAATACTTCTATGAATTCCTGTCTTTCGCTCCCTGGATAAAGGCATCATGGCAGATCC
AACCGTCAATGTCCCTCTGCTGGGAACAGTGCCTCACAAGGCATCAGTTGTTCAAGTTGGTTTC
CCATGTCTTGGAACACAGGATGGGGTGGCAGCATTTGAAGTGGATGTGATTGTTATGAATTCG
AAGGCAACACCATTTCTCCAAACACCTCAAAATGCTATCTTCTTTAAACATGTCAACAAGCTGA
GTGCCCAGGCGGGTGCCGAAATGGAGGGCTTTTGTAAATGAAAGACGCATCTGCGAGTGTCTGA
TGGGTTCCACGGACCTCACTGTGAGAAAGCCCTTTGTACCCACGATGTATGAATGGTGGACTT
TGTGTGACTCCTGGTTTCTGCATCTGCCCACCTGGATTCTATGGAGTGAAGTGTGACAAAGCAA
ACTGCTCAACCACCTGCTTTAATGGAGGGACCTGTTTCTACCCTGGAAAATGTATTTGCCCTCCA
GGACTAGAGGGAGAGCAGTGTGAAATCAGCAAATGCCACAACCCTGTGAAAATGGAGGTAA
ATGCATTGGTAAAAGCAAATGTAAGTGTTCAAAGGTTACCAGGGAGACCTCTGTTCAAAGCCT
GTCTGCGAGCCTGGCTGTGGTGCACATGGAACCTGCCATGAACCCAACAAATGCCAATGTCAA
GAAGGTGGCATGGAAGACACTGCAATAAAAGGTACGAAGCCAGCCTCATACATGCCCTGAGC
GCAGCAGCGCCAGCTCAGGCAGCACACGCCTTCACTTAAAAAGGCCGAGGAGCGGCGGCATC
CACCTGAATCCAATTACATCTGGTGAACCTCCGACATCTGAAACGTTTTAAGTTACACCAAGTTC
ATAGCCTTTGTTAACCTTTTCATGTGTTGAATGTTCAAATAATGTTTACCTTAAAGAATACTG
GCCTGAATTTTATTAGCTTCATTATAAATCACTGAGCTGATATTTACTCTTCTTTTAAGTTTCT
AAGTACGTCTGTAGCATGATGGTATAGATTTTCTGTGTTTCACTGCTTTGGGACAGATTTTATATT
ATGTCAATTGATCAGGTTAAAAATTTTCACTGTGTAGTTGGCAGATATTTTCAAAATTACAATGC
ATTTATGGTGTCTGGGGGCAGGGGAACATCAGAAAGGTTAAATTGGGCAAAAATGCGTAAGTC
ACAAGAATTTGGATGGTGCAGTTAATGTTGAAGTTACAGCATTTTCAATTTTATTGTGAGATAT
TTAGATGTTTGTATCAATTTTAAAAATTTGCTCTTAATTTTAACTCTCAATACAATATATTTGA
CCTTACCATTATTCAGAGATTTCAGTATTAATAAAAAAAATTACACTGTGGTAGTGGCATT
AAACAATATAATATATTCTAAACACAATGAATAAGGGAATATAATGTATGAACCTTTTGCATTG
GCTTGAAGCAATATAATATATTGTAAACAAAACACAGCTCTTACCTAATAAACATTTTATACTG
TTTGTATGTATAAAATAAAGGTGCTGCTTTAGTTTTT

Figure 52

ATGGGCATCGGGCGCAGCGAGGGGGGCGCCGCGGGGCAGCCCTGGGCGTGCTGCTGGCGCTGGGCGCGG
CGCTTCTGGCGGTGGGCTCGGCCAGCGAGTACGACTACGTGAGCTTCCAGTCGGACATCGGCCCGTACCA
GAGCGGGCGCTTCTACACCAAGCCACCTCAGTGCCTGGACATCCCCGCGGACCTGCGGCTGTGCCACAAC
GTGGGCTACAAGAAGATGGTGTGCTGCCAACCTGCTGGAGCAGGACCATGGCGGAGGTGAAGCAGCAGG
CCAGCAGCTGGGTGCCCCCTGCTCAACAAGAACTGCCACGCGGCACCCAGGTCTTCTCTGCTCGCTCTT
CGCGCCCGTCTGCCTGGACCGGCCCCTACCCGTGCTGCTGGCTCTGCGAGGCGGTGCGCGACTCGTGC
GAGCCGGTCAATGCAGTTCTTCGGCTTCTACTGGCCCGAGATGCTTAAGTGTGACAAGTTCCCCGAGGGG
ACGTCTGCATCGCCATGACGCGGCCCAATGCCACCGAAGCCTCCAAGCCCCAAGGCACAACGGTGTGTCC
TCCCTGTGACAACGAGTTGAAATCTGAGGCCATCATTGAACATCTCTGTGCCAGCGAGTTTGGGCTGAGT
TTAAAGATGATTGTGGGTAGCTCCCATAACTCATGCTGCACGCTGGGTCTTCTCATCCCACTCCTCAA
AGCGGCAGGAGCAGGAACTGGGGACTCCTGAGAGAAGGCTTGGATATGGCCTTTTATTACACTTCATCCA
AGGAAATCTGCCCCACCCCTGTGCCCAGGCCCCGATCACGCATGAGGCTAAAGACGGAGGCCACTCCGCTG
GCTCTGGGTAGATCTGCCCCCTGGACTGTTTGCCGACTGCCCGAGCGCCCTCTGCCGGTCTGCAGCTTCC
CACACCACACGGAAGAAGTGGGGAACTGAGGATACATTCTTCTCTCTCCAGGTAAAGGGATTCTCAAT
GAAGGGCTTGTGTGCACCTTCCACACTTAGATACCTCTACTACCTGAAAACCAGCATGCAGCATGTACAT
CAAGAGTACCAGGCACATAGTGCTCAAGTCTGGGCTAATATGCCACCTGCAGAGAGATGTAAAGATGAAG
AAGACAAAGCCATGTTTTCAAAGTGA

Figure 53

41/41

GGCGGGTTTCGCGCCCCGAAGGCTGAGAGCTGGCGCTGCTCGTGCCCTGTGTGCCAGACGGCGGAGCTCCG
CGGCCGACCCCGCGGCCCGCTTTGCTGCCGACTGGAGTTTGGGGGAAGAACTCTCCTGCGCCCCAGA
AGATTTCTTCTCGCGGAAGGGACAGCGAAAGATGAGGGTGGCAGGAAGAGAAGGCGCTTTCTGTCTGCC
GGGGTCGACGCGGAGAGGGCAGTGCCATGTTCTCTCCATCCTAGTGGCGCTGTGCCTGTGGCTGCACC
TGGCGCTGGGCGTGCGCGGCGCGCCCTGCGAGGCGGTGCGCATCCCTATGTGCCGGCACATGCCCTGGAA
CATCACGCGGATGCCCAACCACCTGCACCACAGCACGAGGAGAACGCCATCCTGGCCATCGAGCAGTAC
GAGGAGCTGGTGGACGTGAAGTGCAGCGCCGTGCTGCGCTTCTTCTTCTGTGCCATGTACGCGCCCATTT
GCACCCTGGAGTTCTTGACGACCCCTATCAAGCCGTGCAAGTGGTGTGCCAACGCGCGCGCAGCAGCTG
CGAGCCCCTCATGAAGATGTACAACCACAGCTGGCCCCGAAAGCCTGGCCTGCGACGAGCTGCCTGTCTAT
GACCGTGGCGTGTGCATTTTCGCTGAAGCCATCGTCACGGACCTCCCGGAGGATGTTAAGTGGATAGACA
TCACACCAGACATGATGGTACAGGAAAGGCCTCTTGATGTTGACTGTAAACGCCCTAAGCCCCGATCGGTG
CAAGTGTAAGGAGGTGAAGCCAACTTTGGCAACGTATCTCAGCAAAACTACAGCTATGTTATTTCATGCC
AAATAAAAGCTGTGCAGAGGAGTGGCTGCAATGAGGTCAACAGGTGGTGGATGTAAAGAGATCTTCA
AGTCTCATCACCCATCCCTCGAATCAAGTCCCGCTCATTACAAATTCTTCTTGCCAGTGTCCACACAT
CTGCCCCATCAAGATGTTCTCATCATGTGTTACGAGTGGCGTTCAAGGATGATGCTTCTTGAATTTGC
TTAGTTGAAAAATGGAGAGATCAGCTTAGTAAAGATCCATACAGTGGGAAGAGAGGCTGCAGGAACAGC
GGAGAACAGTTCAGGACAAGAAGAAAAACAGCCGGGCGCACCAGTCGTAGTAATCCCCCAAACCAAGGG
AAGCCTCCTGCTCCCAAACAGCCAGTCCCAAGAAGAACATTAAGGAGTGGCCAGAGAGAACA
AACCCGAAAAGAGTGTGAGCTAACTAGTTTCCAAAGCGGAGACTTCCGACTTCTTACAGGATGAGGCTG
GGCATTGCTGGGACAGCCTATGTAAGGCCATGTGCCCTTGGCCTAACAACTCACTGCAGTGTCTTCA
TAGACACATCTTGACAGATTTTCTTAAGGCTATGCTTCAGTTTTTCTTTGTAAGCCATCACAAGCCATA
GTGGTAGGTTTGCCCTTTGGTACAGAAGGTGAGTTAAAGCTGGTGGAAAAGGCTTATTGCATTGCATTCA
GAGTAACCTGTGTGCATACTCTAGAAGAGTAGGGAAAATAATGCTTGTTACAATTGACCTAATATGTGC
ATTGTAATAATAATGCCATATTTCAAAACAAAACACGTAATTTTTTTACAGTATGTTTTATTACCTTTTGA
TATCTGTGTTGCAATGTTAGTGATGTTTTAAATGTGATGAAAATATAATGTTTTTAAGAAGGAACAGT
AGTGGAAATGAATGTTAAAGATCTTTATGTGTTTATGGTCTGCAGAAGGATTTTTGTGATGAAAGGGAT
TTTTTGAAAAATTAGAGAAGTAGCATATGGAAAATTATAATGTGTTTTTTTACCAATGACTTCAGTTTCT
GTTTTTAGCTAGAACTTAAAAACAAAAATAATAATAAGAAAAATAATAAAAAAGGAGAGGCAGACAAT
GTCGGAATCCTGTGTTTTTGGTTACCTGATTTCCATGATCATGATGCTTCTTGTCAACACCCTCTTAAGC
AGCACAGAAACAGTGAGTTTGTCTGTACCATTAGGAGTTAGGTAATAATTAGTTGGCTAATGCTCAAGT
ATTTTATACCCACAAGAGAGGTATGTCACTCATCTTACTTCCCAGGACATCCACCCTGAGAATAATTTGA
CAAGCTTAAAAATGGCCTTCATGTGAGTGCCAAATTTTGTTTTTCTTCATTTAAATATTTTCTTTGCCTA
AATACATGTGAGAGGAGTTAAATATAAATGTACAGAGAGGAAAGTTGAGTTCACCTCTGAAATGAGAAT
TACTTGACAGTTGGGATACTTTAATCAGAAAAAAGAACTTATTTGCAGCATTTTATCAACAAATTTTCAT
AATTGTGGACAATTGGAGGCATTTATTTTAAAAACAATTTTATTGGCCTTTTGCTAACACAGTAAGCAT
GTATTTTATAAGGCATTCAATAAATGCACAACGCCCCAAGGAAATAAAATCCTATCTAATCCTACTCTCC
ACTACACAGAGGTAATCACTATTAGTATTTTGGCATATTATTCTCCAGGTGTTTGCTTATGCACTTATAA
AATGATTGAACAAATAAACTAGGAACCTGTATACATGTGTTTCATAACCTGCCTCCTTTGCTTGGCCC
TTTATTGAGATAAGTTTTCTGTCAAGAAAGCAGAAACCATCTCATTTCTAACAGCTGTGTTATATTCCA
TAGTATGCATTACTCAACAAACTGTTGTGCTATTGGATACTTAGGTGGTTTCTTCACTGACAATACTGAA
TAAACATCTCACCGGAATTC

Figure 54

GAGGCGCCTTGGGACCGCGTGGGAGCCGACGCCGAACCGAGTAGGGACCGGGACCGCGCGGCGCCGCCG
TCCCCGGCGGGGCCCGGCCCGCGAGCCGAGCGCGCGCCCCGTCGCCACCCGGGCGCGGCTGGATGC
GGCGGGGTCCCCGCGGCGGCGACCCCGGCCCGAGCGCCCGGAGCGCCAGAGGCGGCGTGCAGGGCC
CGGGGACGCGCGCCCTSTBGTGCGCCGAGGCGCGCCCCGAGACAGCCGGGGGCCGCGCCGAGCCGC
CGCCCGCGCTGAGCCCCGGCCCGCGCGCCCGCGCCCGGCGGCGAGCNTGAGCCAGGCCGAGCTGTC
CACCTGCTCCGCGCCGAGACGCGAGCGCATCTCCAGGAGGCTGTGCGCNAGGGCAACACGCAGGAGCT
GCAGTGTGCTGTCAGAACATGACCAACTGCGAGTTCAACGTGAAGTCTCGGGCCCGAGGGCCAGAC
GGCGTGCACCACTCGGTTCATCGTGGCAACCTGGTGTGCTCGTGAAGCTGCTGGTCAAGTTCGGCGCCGAC
ATCCGCTGGCAACCGCGACCGCTGGAGCGCGTGCAMATCGCCGCGTTCGGTGGCCACCAGGACATC
GTGCTCTATCTCATCAACAGGCGAAGTACGCGGCCAGCGCSGGTGTATGCCCGCCGGGACCCCGGACCC
CGGCCCTGCGCCCGCGTCTCTGCTGTACCTTCCCGCCAACTACCTCGGTGCGCGCMCGGCTCGCAGG
CCCCGCCAGAAGGCCCGTGGCAACGGCGAATACGGCGCGTGCCTCMCGCCCCAGGGTC